Masters of Arts in Interdisciplinary Health

School of Rural and Northern Health

Does Exercise-Induced Inflammation Serve a Useful Purpose Across the Adult Age Span?

Sophie Melanie Louise Cartier (M.A.)
Dr. Sandra Dorman (Ph.D.)
Dr. Shelley Watson (Ph.D.)
Dr. Céline Larivière (Ph.D.)

The School of Graduate Studies

Laurentian University, 935 Ramsey Lake Road, Sudbury, ON P3E 2C6

Acknowledgements

I would like to express gratitude to my thesis advisor Dr. Sandra Dorman for accepting me as her student, and for supporting me throughout the entire process. Dr. Dorman provided me with constructive and thorough feedback, and stimulated new thought-provoking ideas during the writing of my major paper. Furthermore, she was actively involved during the writing process by sculpting my major paper through organizing and rearranging paragraphs, and adding some missing and valuable information. Dr. Dorman also assisted me with connecting ideas together, and helped me think about and understand the cause and effect between matters. Importantly, Dr. Dorman was supportive and patient during challenges and difficult times.

I would also like to show appreciation for my committee members, Dr. Shelley Watson and Dr. Céline Larivière, who assisted and guided me throughout my Masters degree. They both provided me with directions regarding my major paper, and evoked new captivating ideas as well. Additionally, Dr. Watson and Dr. Larivière ensured that I was up-to-date with guidelines and deadlines, and were incredibly resourceful. Essentially, I am grateful for their support and patience throughout my obstacles.

Overall, Dr. Dorman, Dr. Watson and Dr. Larivière went over and above for me. I am incredibly blessed and thankful to have had such remarkable and brilliant individuals involved in my Masters degree.

I would also like to acknowledge my parents, André and Louise Cartier, extended family, and friends who supported me while pursuing my Masters degree. Specially, my parents greatly assisted me in so many ways to ensure that I am successful and able to fulfill my dream. I am truly honoured and blessed for having loving parents who provided me with the opportunity to excel academically, and contribute to the advancement of research. Importantly, I am grateful for

their patience and tolerance during the undertaking of my education, and support throughout both my challenges and achievements.

Table of Contents

NOTE: Please see Appendix A for abbreviations on p. 94.

Overview

Inflammation is a protective biological response involving immune cells, blood vessels and molecular mediators, initiated upon the induction of cell injury (Abbas, Lichtman, & Pillai, 2007). The purpose of inflammation is to both eliminate the cause of the injurious agent (Abbas et al., 2007) as well as remove dead cells and tissues, damaged from the initial assault (Lapointe, Frenette, & Côté, 2002), and to initiate tissue repair (Ricciotti & FitzGerald, 2011). Inflammation as an event is a generic response to any injurious insult, which includes exercise-induced injury (Nehlsen-Cannarella et al., 1997). Exercise-induced muscle damage is defined as an injury from a mechanical force applied externally, causing structural stress or strain, resulting in cellular or tissue responses (Mueller & Maluf, 2002).

An acute inflammatory response is sometimes instigated during exercise (Nehlsen-Cannarella et al., 1997); its initiation and magnitude depend upon the degree of physiological stress applied during the exercise bout (McFarlin, Flynn, Stewart, & Timmerman, 2004). Exercise-induced inflammation is typically seen in endurance sports where there is overuse of specific tissues (McFarlin et al., 2004). Physiological stress increases as intensity, duration and internal stimuli (e.g., blood glucose levels) increase (McFarlin et al., 2004). Thus, prolonged and intensive exercises significantly increase the induction of and the magnitude of an inflammatory response (McFarlin et al., 2004). Exercise-induced inflammation also stimulates the activation of the hypothalamic-pituitary adrenocortical (HPA) axis, characterised by elevated levels of cortisol and other mediators, inducing immune suppressive effects and thereby reinstating immune homeostasis (Tsigos & Chrousos, 2002). However, the immunosuppressive effects of the HPA axis may be detrimental to individuals if over-stimulated (Tsigos & Chrousos, 2002).Various methods have been employed in training regimes to counteract this inflammatory response

(Bleakley, McDonough, & MacAuley, 2004; Gleeson, Nieman, & Pedersen, 2004; Quintero, Wright, Fu, & Huard, 2009). Carbohydrate supplementation is one method (Gleeson et al., 2004; McFarlin et al., 2004; Mitchell et al., 1998; Nehlsen-Cannarella et al., 1997; Nieman et al., 2004; Nieman et al., 1998; Scharhag, Myer, Auracher, Gabriel, & Kindermann, 2006). Others, such as cryotherapy (Bleakley et al., 2004) and RICE (rest, ice, compression, and elevation; Quintero et al., 2009), are also commonly used to reduce the exercise-induced inflammatory response under conditions where muscle soreness and/or injuries occur following physical activity (Bleakley et al., 2004; Quintero et al., 2009). The underlying theory is that reducing the inflammation will improve muscle tissue recovery (Bleakley et al., 2004; Quintero et al., 2009).

The exercise-induced inflammatory response is necessary for performance adaptation (Kurtz, Loebig, Anderson, DeMeo, & Campbell, 1999), although, it may also lead to injury and is often associated with pain or discomfort by the individual (Abbas et al., 2007). Considering these two, opposing concepts, it would be valuable to understand the appropriate management of exercise-induced inflammation for both injury prevention and performance gains.

Further complicating this question are external factors, which can enhance or reduce systemic inflammation (Gomez, Nomellini, Faunce, & Kovacs, 2008; Weiskopf, Weinberger & Grubeck-Loebenstein, 2009). In particular, age has significant impacts on both immune function and underlying inflammatory status (Franceschi et al., 2007; Gomez et al., 2008; Weiskopf et al., 2009). For example, aging impacts immune function by weakening immune responses to infections (Gomez, Boehmer, & Kovacs, 2005).

Therefore, the purpose of this paper is to answer two questions: 1) ‘Does Exercise-Induced Inflammation Serve a Useful Purpose?’; and 2) ‘How Does Aging Affect this Process?’ To address these questions, this paper will first: *i)* review the role of inflammation as part of the

innate immune response; *ii)* examine the positive and negative consequences of the exercise-induced inflammatory response; and *iii)* outline the age-related effects on both the immune system and underlying inflammatory status.

Chapter 1: Immunology

1.1 Immune System Overview

The term ‘immunity’ refers to an organism’s protective defences and resistance against infectious disease (Abbas et al., 2007). The immune system encompasses several tissues, including the bone marrow, thymus gland and lymphatic tissue (Abbas et al., 2007). These tissues together with specialized cells and chemical mediators are responsible for immune effects and their combined and coordinated response to the invasion of foreign materials (Abbas et al., 2007). The immune system has two primary functions, which include protecting host cells against infectious agents and distinguishing self from non-self (Abbas et al., 2007).

The immune system consists of two types of immunity: adaptive and innate (Abbas et al., 2007). The adaptive immune response is also known as the ‘acquired’ or ‘specific’ immune response because this branch of the immune system involves specialized cells, which target and eliminate *specific* pathogens and post-infection confers ‘memory’ for that organism, thereby preventing future infections from the same agent (Abbas et al., 2007). The innate immune response is also known as the ‘non-specific’ immune response because this biological cascade is the same, regardless of inciting agent (Abbas et al., 2007). For example, the innate immune system will react the same to repeated exposures to a particular microbe as opposed to responding more aggressively by increasing innate defensive capabilities (Abbas et al., 2007). It is considered to be a more generalized attempt by the body to either eradicate all harmful agents or to control them until an adaptive immune response can be coordinated (Abbas et al., 2007). For the purposes of this paper, we will focus on the innate immune response because inflammation is the main component of the immune system referred to in this paper and is an aspect of innate immunity.

1.2 Innate Immunity

Innate immunity consists of both cellular and biochemical defences whose overall mechanisms underscore non-specific defence mechanisms, and therefore act the same under varying conditions (Abbas et al., 2007). The primary defence mechanisms of the innate immune system, include: 1) physical and chemical barriers (epithelia and antimicrobial products, which are produced at epithelial surfaces); 2) phagocytic cells, such as neutrophils and macrophages, and natural killer (NK) cells; 3) plasma proteins, including the compliment system and other inflammatory mediators; and 4) proteins known as cytokines, which control and synchronize cells of the innate immune response (Abbas et al., 2007). Various cytokines, often referred to as interleukin (IL) followed by a number to discriminate between them (Abbas et al., 2007), are discussed in this paper. Thus, table I includes a list of cytokines mentioned in this paper along with their function(s) and the primary cell(s) that produce them. Some of these defence mechanisms are continuously present as safeguards, even before microbial contact, such as epithelial surfaces (the skin and lining of the gastrointestinal and respiratory tracts), lysozymes, acidic pH or peristalsis (Abbas et al., 2007). Other defences of innate immunity, including phagocytes and the complement system, are circulating but inactive until they are triggered to respond, via other sequelae (Abbas et al., 2007). These mechanisms, although primed, will not discriminate between instigating agents (Abbas et al., 2007).

Table I: Cytokines, Primary Cell Source, and General Biological Roles

Cytokine	Primary Cell Source	General Biological Roles
IL-1	Activated macrophages (Abbas et al., 2007).	Mediates innate inflammatory responses (pro-inflammatory); Stimulates the synthesis of endothelial cell adhesion molecules, C-reactive protein by the liver, and neutrophils by the bone marrow (Abbas et al., 2007). Instigates the breakdown of damaged muscle tissues (Cannon & St. Pierre, 1998).

IL-1Rα	Activated macrophages (Petersen & Pedersen, 2006).	Induces anti-inflammatory effects; Inhibits the actions of IL-1 (Petersen & Pedersen, 2006).
IL-4	T lymphocytes (Abbas et al., 2007) and B lymphocytes (Opal & DePalo, 2000).	Induces anti-inflammatory effects; Inhibits macrophage activation mediated by INF-γ (Abbas et al., 2007), the expression and release of pro-inflammatory cytokines (IL-1, IL-6, IL-8, and TNF-α), and macrophage functions (cytotoxic activity and nitric oxide synthesis) (Opal & DePalo, 2000). Stimulates the production of IL-1Rα (Opal & DePalo, 2000).
IL-6	Activated macrophages, endothelial cells, fibroblasts, and T cells (Abbas et al., 2007).	Induces pro- and anti-inflammatory effects (Petersen & Pedersen, 2005); Pro: Stimulates the synthesis of C-reactive protein by the liver (Abbas et al., 2007), activates the HPA axis (Tsigos & Chrousos, 2002), and increases plasma concentrations of ACTH (via pituitary) (Dunn, 2000). Anti: Stimulates the synthesis of anti-inflammatory mediators (IL-1Rα and IL-10), and inhibits TNF-α production (Petersen & Pedersen, 2006).
IL-8	Activated macrophages (Waugh & Wilson, 2008).	Pro-inflammatory chemokine (Waugh & Wilson, 2008). Neutrophil recruitment and degranulation (Waugh & Wilson, 2008), and neutrophil activation (Baggiolini & Clark-Lewis, 1992).
IL-10	Activated macrophages (Abbas et al., 2007).	Induces anti-inflammatory effects (Abbas et al., 2007). Inhibits the functions of activated macrophages (Abbas et al., 2007).
IL-12	Activated macrophages (Abbas et al., 2007).	Induces pro-inflammatory effects; Activates and enhances the cytotoxic functions of NK cells (Abbas et al., 2007). Links innate and adaptive immunity together (Abbas et al., 2007).
IL-13	T lymphocytes (Abbas et al., 2007).	Induces anti-inflammatory effects; inhibits IL-1 and TNF-α synthesis, and increases IL-1Rα production (Watson et al., 1999).
TNF-α	Activated macrophages, NK cells, and T lymphocytes (Abbas et al., 2007).	Induces pro-inflammatory effects; stimulates the recruitment of neutrophils and monocytes to the inflammatory site, and activates these cells (Abbas et al., 2007). Induces insulin resistance (Peppa et al., 2010). Instigates the breakdown of damaged muscle tissues (Cannon & St. Pierre, 1998).
		Induces pro-inflammatory effects; activates macrophages (Abbas et al.,

INF-γ	NK cells and T lymphocytes (Abbas et al., 2007).	2007) and their functions (tumour cell cytotoxicity, antimicrobial activity, and killing of intracellular pathogens (Young and Hardy, 1995). Stimulates NK cells to activate macrophages (Abbas et al., 2007).

Adapted from Abbas et al., 2007

1.2a Cells of the Innate Immune Response System

The main effector cells of the innate immune system are: macrophages, NK cells and neutrophils (Abbas et al., 2007). These immune cells originate from the bone marrow and circulate in the blood (Abbas et al., 2007). Macrophages, NK cells and neutrophils are described below.

Macrophages are phagocytic cells that have one nucleus; therefore, are also called mononuclear phagocytes (Abbas et al., 2007). These cells circulate in the blood as monocytes, and mature into macrophages in the tissues, where they may be activated (Abbas et al., 2007). Macrophage activation entails phagocytosis as well as mediator release and adaptive immune system activation (Abbas et al., 2007).

NK cells are related to a cell lineage of the adaptive immune system called lymphocytes (Abbas et al., 2007). The blood and spleen contain 5% to 20% of these cells and they are uncommon in other lymphoid organs (Abbas et al., 2007). NK cells continuously cycle from the blood into the tissues and back to the blood through the lymphatic system (Lanier, 2008). The functional roles of NK cells include recognizing infected and/or stressed cells and responding through direct killing of these cells and secreting inflammatory cytokines (Abbas et al., 2007). Furthermore, these cells may activate macrophages inducing phagocytosis and further secretion of inflammatory cytokines, including interferon-gamma (INF-γ) (Abbas et al., 2007).

Neutrophils, also phagocytes, are abundant in the blood; however, they are short lived (circulation time of about 6 hours) and not found in normal, healthy tissues (Abbas et al., 2007;

Janeway, Travers, Walport, & Shlomchik, 2001). Neutrophils are activated during an injurious event wherein they are recruited to the site(s) of innate immune activation and actively ingest microbes and/or dead host cells (Abbas et al., 2007). Under these conditions of activation, neutrophils also produce and secrete cytokines contributing to the coordination of an ongoing innate response (Abbas et al., 2007).

1.2b Inflammation

Inflammation is an important component of the innate immune response. It is initiated by tissue damage, which then activates the innate immune cells (Janeway et al., 2001). The inflammatory response has three critical roles in host defence and recovery (Janeway et al., 2001). These roles include: 1) the recruitment of additional cells and molecules to the site of inflammation; 2) the creation of a physical barrier to prevent the spread of infectious agents; and 3) the removal of dead tissues and the repair of injured tissues (Janeway et al., 2001).

The inflammatory process has been well described and is characterized by pain, redness, heat, and swelling at the active site (Janeway et al., 2001). Injured and dying cells will release inflammation-inciting molecules, including cytokines, prostaglandins and pain effectors, which together initiate a sequence of tissue responses (Janeway et al., 2001). The initial release of inflammatory mediators include lipids, such as prostaglandins, leukotrienes and platelet activating factor, produced through enzymatic pathways responsible for degrading membrane phospholipids (Janeway et al., 2001). However, responding leukocytes subsequently produce and secrete more cytokines and chemokines, enhancing and modifying the inflammation (Janeway et al., 2001).

The first effect of inflammation is vasodilation and increased endothelial permeability (Janeway et al., 2001). These blood changes will increase the amount of total blood flow locally

with a concurrent decrease in the *rate* of blood flow (Janeway et al., 2001). Vasodilation contributes to the physical signs of heat and redness; combined with an increase in permeability, more fluid will escape the vessels into the surrounding tissue contributing to the swelling and pain induction (as tissues are stretched; Janeway et al., 2001). These inflammatory mediators will also induce local endothelial cells to up-regulate their expression of adhesion molecules (Abbas et al., 2007). The combined decrease in blood flow rate, increased permeability, and the expression of adhesion molecules facilitates the process of *extravasation*; that is, the binding of leukocytes to the endothelium and their subsequent migration out of the blood and into the area of tissue damage (Janeway et al., 2001). A sub-class of cytokines, called chemokines, will help to coordinate this migration, by creating a concentration gradient (Abbas et al., 2007). That is, the concentration of chemokines will be highest where the most cell damage and death occurred (i.e., where they are released) and the chemokine concentration will be the lowest further away from the injury (Abbas et al., 2007). This chemical gradient provides a mechanism by which the white blood cells can move towards the area of damaged tissue (Abbas et al., 2007). Neutrophils are classically the first cells to migrate to the site of inflammation followed by macrophages and other leukocytes, such as lymphocytes, which can also be drawn to the site during later stages of ongoing inflammation (Janeway et al., 2001).

In addition to the inflammatory mediators outlined above, when a cell is damaged or undergoing necrosis, the cell releases substances called damage-associated molecular patterns (DAMPs), also called ‘alarmins’ (Abbas et al., 2007; Newton & Dixit, 2012). Cells of the innate immune system recognize and bind DAMPs via pattern recognition receptors (PRRs) expressed on their plasma membrane (Abbas et al., 2007).

DAMPs are normally located inside cells and include: intracellular proteins, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), nucleotides, adenosine triphosphate (ATP), and uric acid (Newton & Dixit, 2012; Srikrishna & Freeze, 2009). An innate immune response mediated only by DAMPs is called 'sterile inflammation' because only the damaged tissues initiate the inflammation, as opposed to, and in absence of, pathogenic infections (Srikrishna & Freeze, 2009).

PRRs are expressed by a variety of cell types, including neutrophils, macrophages, dendritic cells and endothelial cells (Abbas et al., 2007). PRRs are connected to intracellular signal transduction pathways responsible for initiating cellular responses, including the production of inflammatory mediators, defence mechanisms against microbes, and repair of damaged tissues (Abbas et al., 2007). Specifically, many PRRs activate transcription factors, such as nuclear factor kappa B (NF-κB), activator protein-1 (AP-1), cAMP response element-binding protein (CREB), CCAAT-enhancer binding protein (c/EBP), and interferon regulatory factor (IRF), once bound by DAMPs (Newton & Dixit, 2012). Activation of these transcription factors stimulates genes encoding innate responses, including the recruitment and activation of leukocytes in the elimination of foreign substances and debris (Newton & Dixit, 2012). The major classes of PRRs include toll-like receptors (TRLs), c-type lectins, scavenger receptors, n-formyl met-leu-phe receptors, nod-like receptors (NLRs), and caspase activation and recruitment domain (CARD)-containing proteins (Abbas et al., 2007). In addition to the local effects described above, the inflammatory response also induces systemic changes (Abbas et al., 2007; Newton & Dixit, 2012).

1.3 Systemic Inflammatory Effects

1.3a Plasma Proteins

The combined release of inflammatory mediators from damaged/dying cells (Newton & Dixit, 2012) and infiltrating/activating immune cells allow these molecules to spill out into the larger circulatory system (Abbas et al., 2007). Principally, the production of cytokines, including IL-1 and IL-6 from macrophages, stimulate the activation of a group of proteins produced by the liver, called the Acute-Phase Proteins (Abbas et al., 2007). Acute-phase proteins include serum amyloid A, fibrinogen, complement components C3 and C4 and C-Reactive protein (CRP), amongst others (Samols, Agrawal, & Kushner, 2002).

Increased circulating inflammatory cytokines enhance the production and release of these proteins from the liver, whose levels then rise in the blood and induce subsequent effects (Abbas et al., 2007). For example, CRP plasma levels under normal conditions are generally less than 3mg/L; however, during acute inflammation, levels can increase up to a 1000-fold (Abbas et al., 2007). One consequence of the production of these systemic proteins is the activation of the HPA axis (Nehlsen-Cannarella et al., 1997; Tsigos & Chrousos, 2002).

1.3b The Hypothalamic-Pituitary Adrenocortical Axis

The HPA axis is a major component of the neuroendocrine system that controls reactions to stress and regulates many body processes, including the immune system (Nehlsen-Cannarella et al., 1997; Tsigos & Chrousos, 2002). The HPA axis is a neuro-hormonal pathway regulated by the central nervous system (CNS) and its components include: the hypothalamus, the anterior pituitary gland, and the adrenal glands whose parts include the adrenal cortex and the adrenal medulla (Mastorakos, Pavlatou, Diamanti-Kandarakis, & Chrousos, 2005; Pavlov, Wang, Czura, Friedman, & Tracey, 2003). The CNS primarily regulates the HPA axis through the hormones

corticotropin-releasing hormone (CRH) and arginine-vasopressin (AVP; Mastorakos et al., 2005). Parvicellular and magnocellular neurons located in the paraventricular nucleus (PVN) of the hypothalamus synthesize CRH and AVP, which are simultaneously secreted into the hypophyseal portal blood system during stress (Mastorakos et al., 2005; Pavlov et al., 2003). CRH subsequently stimulates the anterior pituitary gland to synthesize adrenocorticotropic hormone (ACTH), which then activates the production and secretion of glucocorticoids including cortisol, from the adrenal cortex (Mastorakos et al., 2005; Pavlov et al., 2003).

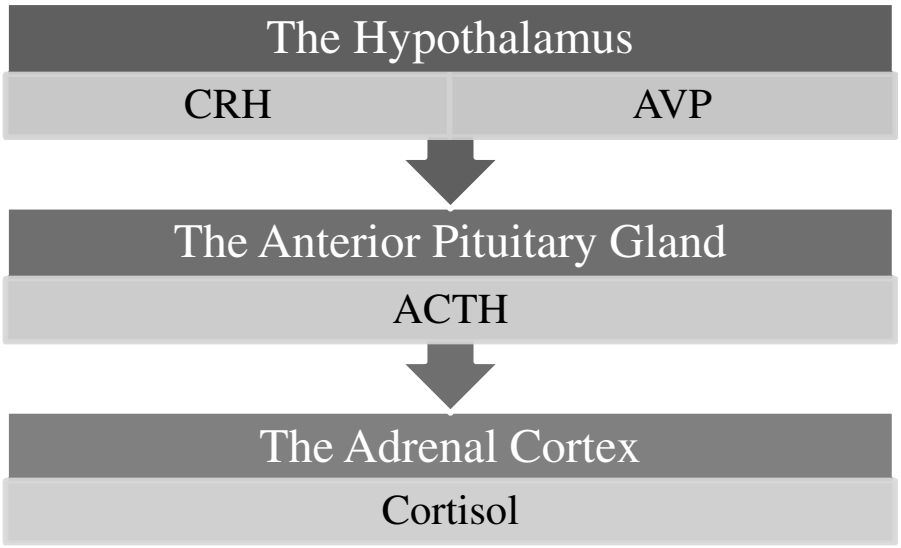

Figure 1:The Hypothalamic-Pituitary Adrenocortical Axis

CRH primarily induces the secretion of ACTH and may exert this function alone; whereas, AVP cannot stimulate ACTH secretion alone, but synergizes with CRH providing additive effects (Mastorakos et al., 2005). The catecholamines epinephrine and norepinephrine are other stress hormones also secreted by the adrenal glands, specifically, the adrenal medulla, (Cosentino et al., 2002) in response to CRH (Karalis, Muglia, Bae, Hilderbrand, & Majzoub, 1997) and upon activation of the HPA axis (Chrousos, 1995). Catecholamines are key hormones in activating the fight or flight response (Goldstein, 2010), characterized by heightened arousal, accelerated motor

reflexes, increased alertness, attention, and cognitive function, as well as decreased appetite and sexual arousal, and increased pain tolerance (Chrousos, 1995). The fight or flight response allows organisms to cope successfully with stressors (Chrousos, 1995). An inflammatory response is considered a stressor; therefore it will concurrently activate the HPA axis with subsequent catecholamine production (Tsigos & Chrousos, 2002).

1.4 The Hypothalamic-Pituitary Adrenocortical Axis and the Immune System

In addition to CRP-activation of the HPA axis, the inflammatory cytokines, tumour necrosis factor-alpha (TNF-α), IL-1, and IL-6, are also potent stimulators of the HPA axis, synergistically or alone (Tsigos & Chrousos, 2002). Each cytokine induces a positive feedback loop, causing enhancement of secretion of all cytokines; TNF-α and IL-1 stimulate each other and both induce IL-6 release (Mastorakos et al., 2005). IL-6 is the predominant cytokine in activating the HPA axis, particularly in conditions of chronic inflammatory stress (Tsigos & Chrousos, 2002).

Signalling of these cytokines along with those of the nervous and endocrine systems converge at the hypothalamic PVN to stimulate CRH secretion (Flaster, Bernhagen, Calandra, & Bucala, 2007). CRH subsequently induces the secretion of ACTH, which stimulates the synthesis and secretion of cortisol causing widespread immunosuppressive effects (Flaster et al., 2007), concluding in a negative feedback loop, reinstating immune homeostasis (Tsigos & Chrousos, 2002).

Cortisol induces its immunosuppressive effects by permeating immune cell membranes and binding to glucocorticoid receptors forming a cortisol-glucocorticoid receptor complex (Flaster et al., 2007). The inflammatory response is subsequently inhibited by the following: cortisol down-regulates gene expression of the pro-inflammatory mediators; and up-regulates

gene expression of anti-inflammatory agents (Pavlov et al., 2003). The cytokines TNF-α, IL-1, IL-6, IL-8, IL-12 and INF-γ, and other inflammatory mediators are all inhibited at the level of gene transcription through suppression of AP-1 and NF-κB, the latter being the most notable since NF-κB is essential for regulating the production of cytokines (Flaster et al., 2007; Pavlov et al., 2003). The synthesis of anti-inflammatory cytokines, including IL-4 and IL-10 is then activated (Pavlov et al., 2003). Furthermore, cortisol suppresses the immune response through decreased migration of leukocytes to the site of infection or tissue injury by inhibiting the expression of cell adhesion molecules (Flaster et al., 2007; Pavlov et al., 2003). Lastly, cortisol regulates the magnitude of the inflammatory response by stimulating apoptosis of leukocytes (Flaster et al., 2007).

In this chapter, an overview of the immune system was described and the HPA axis was introduced. Emphasis was placed on the innate immune system because inflammation is the main component of the immune system that is relevant to this paper and is an aspect of innate immunity. The following chapter pertains to inflammation with regards to exercise, and the advantages and disadvantages of the exercise-induced inflammatory response.

Chapter 2: Exercise-Induced Inflammation; Advantages and Disadvantages

2.1 Exercise-Induced Inflammation

Muscle soreness and injury typically result from endurance exercise leading to the development of an acute inflammatory response during and after physical activity (Nehlsen-Cannarella et al., 1997). The magnitude of the immune response is dependent on the degree of physiological stress applied during exercise (McFarlin et al., 2004). Physiological stress increases during physical activity depending on: intensity; duration; and internal stimuli (e.g., blood glucose levels; McFarlin et al., 2004). Prolonged and intensive endurance exercise significantly increases the magnitude of the inflammatory immune response (McFarlin et al., 2004) and this inflammatory response includes the production of local and systemic inflammatory cytokines, (including IL-1, IL-6, IL-8 and TNF-α) and acute-phase proteins (including CRP), with the amount produced also dependent on exercise intensity and therefore level of tissue injury (Nehlsen-Cannarella et al., 1997; Nieman, 1997). In response to the exercise-induced inflammatory reaction, the HPA axis is activated, as physical activity and inflammation are stressors to the body (Mastorakos et al., 2005).

Studies have shown that following prolonged and intensive endurance training, plasma cortisol, IL-6, epinephrine and norepinephrine, and white cell counts are all significantly elevated (Mitchell et al., 1998; Nehlsen-Cannarella et al., 1997; Nieman et al., 2004; Nieman et al., 1998; Scharhag et al., 2006). These exercise-associated immune-enhanced and suppressive changes may last between 3 to 72 hours (Nieman, 2003). The immunosuppressive changes induced by exercise are perceived to have harmful effects, thus researchers have attempted to blunt the extent of the exercise-induced inflammatory response (Nieman, 2003). A common method is through the use of carbohydrate supplementation, because internal stimuli (i.e., blood

glucose levels) may be controlled to a certain degree during exercise by increased glucose consumption, such as orange juice or Gatorade for example (Gleeson et al., 2004; McFarlin et al., 2004; Mitchell et al., 1998; Nehlsen-Cannarella et al., 1997; Nieman et al., 2004; Nieman et al., 1998; Scharhag et al., 2006). Cryotherapy, which is the decrease in tissue temperature through the use of ice or ice baths for example (Bleakley et al., 2004), and RICE are other common methods used to blunt the exercise-induced inflammatory response to treat soft-tissue injuries and/or muscle soreness following physical activity (Quintero et al., 2009). The attenuation of the exercise-induced inflammatory response is discussed further in section 2.4.

Muscle damage from exercise is often caused by eccentric (i.e., lengthening of muscles) muscle actions rather than concentric (i.e., shortening of muscles) or isometric (i.e., no change in muscle length) muscle actions because eccentric muscle contractions induce greater tension (Peake, Nosaka, & Suzuki, 2005). Thus, scientists primarily use eccentric exercises to study exercise-induced muscle damage and the subsequent inflammatory response (Paulsen, Ramer Mikkelson, Raastad, & Peake, 2012).

Generally, following this type of exercise, neutrophils quickly enter the circulation and then enter damaged muscle tissues remaining there for up to 24h (Peake et al., 2005). The mobilization of NK cells is also noted, and during and immediately after eccentric exercise, increases in pro-inflammatory cytokines are measured in the bloodstream (Peake et al., 2005). Within one day post exercise-challenge, macrophages replace neutrophils in damaged muscle tissues, with the continued production of pro-inflammatory cytokines that are detectable up to 14 days post eccentric exercises (Peake et al., 2005). These inflammatory responses are significant because they regulate the acute-phase protein response and coordinate the elimination of muscle fragments (Peake et al., 2005). Damaged muscle tissues are degraded by neutrophils and

macrophages by releasing reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Peake et al., 2005). Up to 5 days following exercise, injured muscle cells express the pro-inflammatory cytokines IL-1β and TNF-α, which are involved in initiating the breakdown of damaged muscle tissues (Peake et al., 2005). After exercise, IL-6 is also expressed in muscle tissues (Peak et al., 2005). This cytokine is considered to be both a pro- and anti-inflammatory mediator (Pedersen, Steensberg & Schjerling, 2001); however, some researchers argue that it should only be classified as an anti-inflammatory cytokine (Steensberg, Fischer, Keller, Møller, & Pedersen, 2003). As a pro-inflammatory cytokine, IL-6 stimulates the secretion of CRP from the liver (Siewert et al., 2004). As an anti-inflammatory cytokine, IL-6 induces the production of anti-inflammatory mediators such as IL-1Rα and IL-10, and suppresses the production of TNF-α (Petersen & Pedersen, 2006).

2.2 Exercise Intensity and Inflammation

2.2a Defining Exercise Intensities

Research concerning the relationship between exercise intensity and the immune response has mainly been conducted with regards to prolonged and intensive endurance training (Plowman & Smith, 2008). Specifically, scientists have studied the effects of medium duration (<45 minutes), moderate- to high-intensity aerobic/endurance exercise, and prolonged (1-3 hours), moderate- to high-intensity aerobic/endurance exercise on the immune response (Plowman & Smith, 2008). It should be noted that defining exercise of medium- and prolonged-duration, and exercise of moderate- and high-intensity is challenging as different values are used in the literature. Various definitions of exercise of medium duration are <45 minutes (Plowman & Smith, 2008) and <120 minutes, or 30-180 minutes (Hackney, 2006). Defining exercise of medium-duration is sometimes adjusted according to the intensity. For example, if the exercise

intensity is moderate (35-70% VO_{2max}) (Hackney, 2006), exercise of medium-duration may be considered as <45 minutes (Plowman & Smith, 2008), or 30-180 minutes (Hackney, 2006). If the exercise intensity is high (>70% VO_{2max}) (Hackney, 2006), exercise of medium duration may be considered as either <45 minutes (Plowman & Smith, 2008), or <120 minutes (Hackney, 2006). Exercise of prolonged duration is typically defined as >90 minutes (Gleeson, 2007), or 1-3 hours (Plowman & Smith, 2008). Moderate-intensity exercise is commonly defined as 35-70% VO_{2max}, and high-intensity training is generally defined as >70% VO_{2max} (Hackney, 2006).

For the purpose of this paper, medium-duration and prolonged exercise, and moderate- and high-intensity exercise will be defined as outlined in Table II.

Table II: Exercise Durations and Intensities

Variable	Typical Duration	Intensity (% VO_{2max})
Medium-Duration, Moderate-Intensity	30-45 minutes	35-70% VO_{2max}
Medium-Duration, High-Intensity	45-120 minutes	>70% VO_{2max}
Prolonged-Duration, Moderate-Intensity	1-3 hours	35-70% VO_{2max}
Prolonged-Duration, High-Intensity	1-3 hours	>70% VO_{2max}

These are my definitions of exercise durations and intensities, which are adapted from Hackney, 2006, and Plowman & Smith, 2008.

2.2b Immune Responses to Different Exercise Intensities and Durations

As a characteristic of the immune response, exercise induces leukocytosis, which is an increase in the number of white blood cells in the blood (Plowman & Smith, 2008). Leukocytosis continues for at least 2-6 hours following physical activity (Plowman & Smith, 2008). Therefore, the magnitude of the immune response may be measured in part by the number of leukocytes accumulating in the blood during and immediately after exercise, and during the post-exercise recovery period (Plowman & Smith, 2008). The body of knowledge pertaining to the systemic

inflammatory response during and immediately after exercise, and during post-exercise recovery is greater than the body of knowledge relating to the local inflammatory response in muscle tissues during and immediately after exercise, and during post-exercise recovery (Peake et al., 2005). This situation is currently the case because, drawing blood samples from subjects is less invasive than taking muscle biopsies (Peake et al., 2005). Additionally, it is easier to measure the number of leukocytes in blood samples than to perform "immunohistochemical staining and gene expression studies in muscle samples" (Peake et al., 2005, p. 66). It is also easier to compare the magnitude of the exercise-induced inflammatory response to different types of exercise intensities and durations when examining systemic inflammation (Peake et al., 2005). Furthermore, even though immune cell numbers does not represent the full spectrum of the exercise-induced inflammatory response, "a large volume of data is available relating to changes in the number of neutrophils, monocytes, and NK cells" in the blood during and immediately after exercise, and during post-exercise recovery (Peake et al., 2005, p. 67). Normal ranges for circulating neutrophils, monocytes, and NK cells in the plasma are: 50-70%, 3-7%, and 10-19%, respectively (Elgert, 1996). Since leukocytosis continues for approximately 2-6 hours following physical activity (Plowman & Smith, 2008), measuring leukocyte changes from before exercise to 14 days post-exercise would be difficult. Much of the data available regarding timeframe following physical activity includes 2-6 hours post-exercise (Plowman & Smith, 2008). Thus, data that document leukocyte changes from before exercise to 14 days post-exercise are lacking in the literature. Sometimes, knowledge regarding the timeframe in changes of leukocyte numbers in the plasma is unknown (Plowman & Smith, 2008); hence, will not be described below.

Physical activity can also indirectly induce immediate or long-term (3-72 hours) effects on the overall *function* of the immune cells (Plowman & Smith, 2008); this function is assessed by measuring their defence mechanism activities (Singh, Failla, & Deuster, 1994). For example, the respiratory burst of phagocytes, which is discussed later on, is measured through a respiratory burst assay (Singh et al., 1994). Natural killer cell activity (NKCA) is commonly determined via flow cytometry (Kane, Ashton, Schmitz, & Folds, 1996). The overall *function* of the immune cells are either enhanced or suppressed, *depending on the intensity and duration of the exercise bout* (Plowman & Smith, 2008). That is, in general: moderate intensity exercise appears to enhance immune cell function while high-intensity exercise suppresses immune function (Gleeson, 2007; Plowman & Smith, 2008). Duration of exercise appears less significant (Plowman & Smith, 2008). Immune suppression may last longer than 3-72 hours if "periods of intensified training" persist for one week or more (Gleeson, 2007, p. 698). These 'functional effects' are thought to occur through activation of the HPA axis; stimulated by the exercise-induced inflammatory response (Mastorakos et al., 2005).

An enhanced immune cell function suggests that exercise-induced inflammatory responses are beneficial to the individual. However, a suppressed immune cell function would indicate that the exercise-induced inflammatory response is causing harmful effects to the individual. Table III summarizes the available evidence on the effects of different exercise intensities and durations, including: the percentage of immune cells in the blood during exercise, post-exercise and recovery; and immune cell functioning. The percentage of immune cells mobilized in the blood may provide an estimate of the magnitude of the exercise-induced inflammatory response. An interpretation of the data is also provided in table III. The purpose for including these data are as follows: *i)* to provide guidelines/references for the researcher to

answer her research question and draw conclusions upon, and *ii)* to provide the reader with evidence and reasoning for the researcher's answers, reasoning, and conclusions.

Table III: Response of Immune Cells to Different Exercise Durations and Intensities

Variable	% Cells	Recovery	Immune Cell Functions
< Total Leukocytes >			
Med.-Dur., Mod.-Inten.	↑ 0-40%	Unknown	N/A
Med.-Dur., High-Inten.	↑ 50%	↑ 50-100% 2 hr post-exercise	N/A
Prol.-Dur., Mod.-Inten.	↑ 25-50%	↑ 25-65% 2 hr post-exercise	N/A
Prol.-Dur., High-Inten.	↑ 200-300%	↑ 200-300% 2-6 hr post-exercise	N/A
<Neutrophils>			
Med.-Dur., Mod.-Inten.	↑ 30-50%	Unknown	Enhanced
Med.-Dur., High-Inten.	↑ 30-150%	Unknown up to 2 hr post-exercise 25-100% 2-4 hr post-exercise (returns to baseline levels after 2-4 hr post-exercise)	Enhanced
Prol.-Dur., Mod.-Inten.	↑ 20-50 %	↑ 50-150% 2 hr post-exercise	Enhanced
Prol.-Dur., High-Inten.	↑ 300%	↑ 300-400% 2-6 hr post-exercise	Suppressed
<Monocytes>			
Med.-Dur., Mod.-Inten.	No Change	Unknown	Enhanced
Med.-Dur., High-Inten.	↑ 0-20%	↑ 0-50% 2 hr post-exercise (returns to baseline levels after 2 hr)	Enhanced
Prol.-Dur., Mod.-Inten.	No Change	No Change	Enhanced
Prol.-Dur., High-Inten.	↑ 50-100%	↑ 50-100% 2-3 hr post-exercise	Unclear - Some Enhanced, Some Suppressed
<NK Cells>			
Med.-Dur., Mod.-Inten.	↑ 0-50%	Normal by 1 hr post-exercise	NKCA enhanced, then returns to pre-exercise activity once NK cell count returns to baseline levels (returns to normal activity by 1 hr post-

			exercise)
Med.-Dur., High-Inten.	↑ 100-200%	↓ 40% 2-4 hr post-exercise (returns to baseline levels after 2-4 hr post-exercise)	NKCA enhanced during and immediately after exercise, then suppressed for 2-4 hr post-exercise recovery, and returns to pre-exercise activity once NK count returns to baseline levels (returns to normal activity after 2-4 hr)
Prol.-Dur., Mod.-Inten.	↑ 70-100%	↓ 0-50% 1-2 hr post-exercise	NKCA enhanced during and immediately after exercise, then suppressed for 1-2 hr post-exercise recovery, and returns to pre-exercise activity once NK cell count returns to baseline levels (returns to normal activity after 1-2 hr)
Prol.-Dur., High-Inten.	↑ 100-200%	↓ 30-60% 1-2 hr post-exercise	NKCA enhanced during and immediately after exercise, then suppressed for 1-2 hr post-exercise recovery, and returns to pre-exercise activity once NK cell count returns to baseline levels (returns to normal activity after 1-2 hr)

Adapted from Plowman & Smith, 2008

Legend

Med.-Dur., Mod.-Inten. = Medium-Duration, Moderate-Intensity
Med.-Dur., High-Inten. = Medium-Duration, High-Intensity
Prol.-Dur., Mod.-Inten. = Prolonged-Duration, Moderate-Intensity
Prol.-Dur., High-Inten. = Prolonged-Duration, High-Intensity
NKCA = Natural Killer Cell Activity

Based upon the summary presented in Table III, it appears that medium-duration, moderate-intensity exercise induces the lowest immune response while prolonged-duration, high-

intensity training elicits the largest immune response (Plowman & Smith, 2008). Additionally, medium-duration, high-intensity and prolonged-duration, moderate-intensity exercise both induce a greater inflammatory response during or immediately after exercise and recovery compared to medium-duration, moderate-intensity training (Plowman & Smith, 2008). This effect means that, as one variable increases (either intensity *OR* duration), the magnitude of the exercise-induced inflammatory response increases as well (Plowman & Smith, 2008). However, intensity seems more significant than duration; meaning, an increase in intensity alone (i.e., without an increase in duration) elicits a greater inflammatory response than an increase in duration alone (i.e., without an increase in duration; Plowman & Smith, 2008). The effects of prolonged-duration exercise seem significant when combined with high-intensity training, as the largest inflammatory response is instigated when an increase in duration is added to an increase in intensity (Plowman & Smith, 2008). In other words, it appears that the magnitude of the exercise-induced inflammatory response increases exponentially when an increase in intensity is combined with an increase in duration (Plowman & Smith, 2008).

The data in table III show variations in effects with respect to immune function, which is also significant (Plowman & Smith, 2008). In general, medium-duration, moderate-intensity, medium-duration, high-intensity, and prolonged-duration, moderate-intensity exercise all enhanced immune cell functions; whereas, prolonged-duration, high-intensity training suppressed the functioning of immune cells (Plowman & Smith, 2008).

2.3 The Cortisol Response to Exercise

Normally, a negative feedback regulates the secretion of cortisol: enhanced circulation of cortisol stimulates the anterior pituitary to decrease the secretion of ACTH (Hill et al., 2008). The hypothalamus may also be stimulated by increased levels of ACTH and/or cortisol, inducing

a decrease in the secretion of CRH, also indirectly inhibiting further cortisol release (Hill et al., 2008). Nevertheless, this cortisol inhibition is overridden during periods of prolonged and intensified exercise (Mastorakos et al., 2005). As a result, the hyper-secretion of cortisol is induced due to over-stimulation of the HPA axis (Mastorakos et al., 2005); the mechanism by which this occurs is not fully understood (Hill et al., 2008; Mastorakos et al., 2005).

Cortisol is considered a "slow-acting hormone", which means, its rate of response and secretion is slow and gradual (Plowman & Smith, 2008, p. 40). Defining a specific cortisol pattern to exercise is challenging for two reasons: 1) Exercise-induced elevations in blood concentrations of cortisol is delayed at the onset of physical activity, and 2) During short-duration and/or low- to moderate-intensity training, cortisol is cleared from the bloodstream (Plowman & Smith, 2008). Thus, despite the increase in cortisol secretion, its concentration in the bloodstream decreases (Plowman & Smith, 2008). The increase in cortisol during aerobic/endurance exercise is dependent on the intensity and duration of training (Plowman & Smith, 2008). In the context of short- to medium-duration (45 minutes or less), low- to moderate-intensity exercise (less than or equal to 50% VO_{2max}), the clearance of cortisol surpasses its secretion (Plowman & Smith, 2008). Thus, an increase in the circulating cortisol is not observed during low-moderate intensity exercise (Plowman & Smith, 2008) because the stress level imposed on the metabolic system is low (Chandler & Brown, 2008). In fact, levels of cortisol in the blood decrease steadily at an exercise intensity less than or equal to 50% VO_{2max} (Chandler & Brown, 2008; Plowman & Smith, 2008). The blood concentrations of cortisol rise gradually "with the duration of exercise" (Chandler & Brown, 2008, p.111) or "as time continues" (Plowman & Smith, 2008, p. 40) at exercise intensities >50% VO_{2max}, even though the workload is constant (Chandler & Brown, 2008; Plowman & Smith, 2008). Therefore, low- to moderate-

intensity exercise of short- to medium-duration has immune enhancing properties primarily mediated through the reduction in total circulating cortisol (Plowman & Smith, 2008).

Conversely blood cortisol rises at exercise intensities >50% VO_{2max}, even though the workload is constant (Plowman & Smith, 2008). It is hypothesized that blood concentrations of cortisol increase at exercise intensities greater than 50% VO_{2max} because the energy requirements are higher when performing at these levels (Chandler & Brown, 2008). Cortisol levels are also influenced by the duration of exercise; an increase in the blood concentrations of cortisol is not elicited by short-duration aerobic/endurance exercise (Pedersen & Hoffman-Goetz, 2000). Nonetheless, prolonged, aerobic/endurance exercise (i.e., approximately 1 hour; McConell, Canny, Daddo, Nance, & Snow, 2000) increases cortisol levels in the bloodstream as the aerobic/endurance exercise bout continues (Chandler & Brown, 2008); this increase in blood concentrations of cortisol remains for 2 hours or more (Plowman & Smith, 2008). Thus, increased cortisol secretion causes immunosuppressive effects as outlined in section 2.2b, which means that intense, long-duration exercise has immune suppressive effects (Plowman & Smith, 2008).

2.4 Physiologic Attenuation of the Exercise-Induced Inflammatory Response

The inflammatory response is blunted through carbohydrate supplementation (Gleeson et al., 2004; McFarlin et al., 2004; Mitchell et al., 1998; Nehlsen-Cannarella et al., 1997; Nieman et al., 2004; Nieman et al., 1998; Scharhag et al., 2006). Given that immune suppressive effects of exercise-induced inflammation might be considered to be harmful, researchers have attempted to decrease the immunosuppressive effects of cortisol in conditions where athletes engage in prolonged and intensive endurance exercise (Gleeson et al., 2004; McFarlin et al., 2004; Mitchell et al., 1998; Nehlsen-Cannarella et al., 1997; Nieman et al., 2004; Nieman et al., 1998; Scharhag

et al., 2006). Studies have shown that low blood glucose is associated with HPA axis activation and therefore increased secretion of ACTH, cortisol and catecholamines, such as epinephrine and norepinephrine (McFarlin et al., 2004; Mitchell et al., 1998; Nehlsen-Cannarella et al., 1997; Nieman et al., 2004; Nieman et al., 1998; Scharhag et al., 2006). Furthermore, researchers found that exercising in a glycogen-depleted state induced a decrease in neutrophil function and NK cell activity (Gleeson et al., 2004; McFarlin et al., 2004). Hence, disturbance of immune function may be induced by both glucose depletion and elevation in stress hormone levels (Pyne & Burke, 2000). Carbohydrate ingestion during prolonged and intensive endurance training caused higher plasma glucose levels, and attenuated the rise in cortisol, IL-6 and other cytokines, and leukocytes (McFarlin et al., 2004; Mitchell et al., 1998; Nehlsen-Cannarella et al., 1997; Nieman et al., 2004; Nieman et al., 1998; Scharhag et al., 2006). Finally, carbohydrate supplementation decreased the rise in catecholamines and ACTH, prevented the decrease in neutrophil function, and increased NK cell activity (Gleeson et al., 2004; McFarlin et al., 2004). Recall that stress instigates an inflammatory response and that its magnitude depends on the degree of physiological stress applied (McFarlin et al., 2004). Also, the HPA axis is activated by stressors as well (Tsigos & Chrousos, 2002). Since low blood glucose levels imposes stress on the body, it will elicit an inflammatory response and activate the HPA axis resulting in an increase in white blood cells, and pro- and anti-inflammatory mediators (McFarlin et al., 2004). The ingestion of carbohydrates increase blood glucose levels, which eliminate or decrease the stressor (i.e., low blood glucose levels); therefore, the rise in white blood cells, and pro- and anti-inflammatory mediators are decreased as well (Gleeson & Bishop, 2000). Additionally, immune cells utilize glucose as a source of fuel; hence, a decrease in blood glucose levels will decrease the functions of immune cells (Gleeson & Bishop, 2000). Replenishing blood glucose levels will therefore

increase the functions of immune cells due to the energy availability to exert their functions (Gleeson & Bishop, 2000).

As previously mentioned, cryotherapy (Bleakley et al., 2004) and RICE (Quintero et al., 2009) are also common methods used to blunt the exercise-induced inflammatory response to treat soft-tissue injuries and/or muscle soreness following physical activity (Bleakley et al., 2004; Quintero et al., 2009). Nevertheless, the use of these techniques, including carbohydrate supplementation during physical activity, is questionable (Mirkin, 2014), which is discussed further below; in Chapter 4, section 4.1. This is questionable because, although exercise-induced inflammation has detrimental effects, it may be beneficial to the individual as well; the advantages and disadvantages of the exercise-induced inflammatory response are discussed next.

2.5 Advantages of Exercise-Induced Inflammation

Exercise-induced inflammation has beneficial local and systemic effects to individuals, which are discussed in this section. Locally, the effects of exercise-induced inflammation are direct. However, the systemic effects of the exercise-induced inflammatory response are indirect as they are mediated by the HPA axis once activated by the inflammation.

2.5.a Local Effects

The exercise-induced inflammatory response is essential for repairing damaged muscle tissues and reinstating their structure and physiological function (Ricciotti & FitzGerald, 2011). Skeletal muscles undergoing regeneration are known to contain a high concentration of immune cells, which mediate and coordinate the repair of damaged muscle tissues (Tidball & Villalta, 2010). Immune cells modulate the regenerative capacity of skeletal muscles through the secretion of molecules (e.g., cytokines; Tidball & Villalta, 2010), and by influencing other systems (e.g., endocrine system; Nehlsen-Cannarella et al., 1997; Nieman et al., 1998).

Immune cells secrete or induce the secretion of various growth factors, which assist in repairing and regenerating damaged muscle cells, and adapting to physical activity (Kurtz et al., 1999). For instance, through IL-6 (Mastorakos et al., 2005), the inflammatory response induces the production of growth hormone (GH) by the pituitary gland, stimulating the repair and remodelling of the muscle tissue, and increasing protein synthesis (Nehlsen-Cannarella et al., 1997; Nieman et al., 1998; Volek, 2004). Therefore, this effect not only induces the recovery from the muscle injury, but also causes muscle building for improved performance during subsequent activity (Volek, 2004). Additionally, macrophages secrete insulin-like growth factor 1 (IGF-1), which is implicated in each stage of muscle tissue healing (Kurtz et al., 1999). In fact, the regeneration of skeletal muscles and adaptations to exercise is significantly impaired by low levels or the absence of IGF-1 (Kurtz et al., 1999).

Infiltrating immune cells are also recognized for their role in activating satellite cells (skeletal muscle cell precursors) through secretion of these same mediators; that is, IL-6 (Tidball & Villalta, 2010; Yin, Price, & Rudnicki, 2013) and IGF-1 (Mourkioti & Rosenthal, 2005). Satellite cells are mononucleated, myogenic cells that reside inside skeletal muscle fibres and remain quiescent until activated by stimuli, such as exercise-induced myo-trauma (Hawke & Garry, 2001). Satellite cells play a major role in the growth, repair, and regeneration of skeletal muscles (Tidball & Villalta, 2010). Once activated, these cells proliferate and differentiate into myoblasts, which may then fuse to myofibres already present, or combine together forming new muscle fibres while damaged muscle tissues are removed (Schultz & McCormick, 1994).

2.5.b Systemic Effects

As described above, exercise activates the HPA axis system; although over-stimulation of the HPA axis has negative effects (discussed further below), normal stimulation has positive

systemic effects. Normal stimulation of the HPA axis entails the negative feedback control via cortisol discussed in section 2.3 (Hill et al., 2008). The HPA axis, through the actions of catecholamines, is essential for heightening arousal, accelerating motor reflexes, increasing alertness, attention, and cognitive function, decreasing appetite and sexual arousal, and increasing pain tolerance (i.e., activating the fight or flight response; Chrousos, 1995). Additionally, acute, exercise-induced activation of the HPA axis results in increased heart rate and blood flow and thus, increased oxygen delivery to the exercising muscles (Stratakis & Chrousos, 1995). These physiological changes and the fight or flight response allow individuals to cope successfully with the stress induced by exercise, and perform physical activity optimally (Lundberg, 2005).

The combined production of the catecholamines, epinephrine and norepinephrine, cortisol, and GH stimulated by the exercise-induced inflammatory response also have positive systemic effects including: enhanced mobilization of fuel and improved lifetime health (Plowman & Smith, 2008).

2.5.b.i Mobilization of Energy Reserves

Catecholamines, cortisol, and GH stimulate the mobilization of fuel by stimulating adipose, liver, and skeletal muscle cells (Plowman & Smith, 2008). These hormones bind to receptors on target cells causing the following: a) adipose cells: inhibiting fat storage and inducing lipolysis; b) liver cells: enhancing glycogenolysis; c) skeletal muscle cells: enhancing uptake and utilization of fat and enhanced muscle glycogenolysis (Plowman & Smith, 2008). Circulating IL-6 enhances these effects also stimulating lipolysis and oxidation of fatty acids (Petersen & Pedersen, 2005). These changes are essential for producing ATP energy required for

supporting muscle contraction and maintaining blood glucose levels (because neural tissues may only use glucose as an energy source) (Plowman & Smith, 2008).

Catecholamines simultaneously act on pancreatic alpha- and beta-cells inducing the release of glucagon and suppressing the secretion of insulin respectively (Borer, 2003; Plowman & Smith, 2008). Insulin and glucagon induce antagonistic effects: insulin is responsible for converting glucose into glycogen in the liver and skeletal muscles, and triglycerides in the adipose tissues (Fox, 2009). Whereas, glucagon stimulates the breakdown of glycogen into glucose (glycogenolysis), and also, promotes the breakdown of non-carbohydrate molecules into glucose (gluconeogenesis) (Fox, 2009). Glycogenolysis and gluconeogenesis both result in glucose being secreted into the bloodstream to ensure that blood glucose levels do not drop too low; therefore, sustaining energy for physical activity (Fox, 2009). Thus, the suppression of insulin secretion and the release of glucagon are essential for the mobilization of energy to exert physical activity (Marliss & Vranic, 2002).

2.5.b.ii Improved Lifelong Health

Mediators of the exercise-induced inflammatory response as well as those of the HPA axis are believed to provide significant health benefits, such as lowering the level of systemic inflammation (Handschin & Spiegelman, 2008). Correlations exist between physical inactivity and low-grade systemic inflammation (Petersen & Pedersen, 2005). Likewise, regular, moderate exercise has been shown to reduce or suppress this low-grade systemic inflammatory response (Petersen & Pedersen, 2005). This outcome is explained hypothetically by the following: Exercise induces the secretion of high, circulating levels of IL-6, which may function as both a pro- and anti-inflammatory cytokine (Petersen & Pedersen, 2005). Following physical activity, IL-6 induces its anti-inflammatory effects by stimulating the secretion of anti-inflammatory

mediators, including IL-1 receptor antagonist (IL-1Rα) and IL-10 (Petersen & Pedersen, 2005). IL-1Rα inhibits the actions of IL-1 (Petersen & Pedersen, 2006), and IL-10 inhibits the functions of activated macrophages (Abbas et al., 2007).The anti-inflammatory roles of IL-1Rα and IL-10 are important for regulating innate pro-inflammatory responses (Opal & DePalo, 2000). Additionally, IL-6 controls circulating levels of the pro-inflammatory cytokine TNF-α in the plasma by inhibiting its production from immune cells (Petersen & Pedersen, 2005); again, regulating inflammation (Opal & DePalo, 2000). Low-grade systemic inflammation may be lowered or suppressed by the HPA axis through the secretion of catecholamines and cortisol as these mediators modulate the immune response (Handschin & Spiegelman, 2008). Therefore, the exercise-induced inflammatory response and the subsequent activation of the HPA axis may offer protection against, control, or lessen the symptoms of autoimmune/inflammatory diseases (Petersen & Pedersen, 2005). Cytokines, such as IL-6, produced by skeletal muscle cells followed by their secretion into the bloodstream may also contribute to the beneficial long-term health effects of exercise (Handschin & Spiegelman, 2008).

2.6 Disadvantages of Exercise-Induced Inflammation

Exercise-inducing muscle injury leads to the production of inflammation and hence inflammatory mediators (Nehlsen-Cannarella et al., 1997). These mediators have both local (Coletti, Moresi, Adamo, Molinaro, & Sassoon, 2005) and systemic effects (Angeli, Minetto, Dovio, Paccotti, 2004), which can impact muscle recovery negatively, under prolonged conditions (Coletti et al., 2005; Angeli et al., 2004).

2.6.a Local Effects

Strenuous exercise performed on a daily basis, inducing muscle injury, leads to the repeated and regular production of inflammatory mediators (Gokhale, Chandrashekara, &

Vasanthakumar, 2007). In the immediate vicinity, inflammatory mediators can directly hamper the regeneration of skeletal muscles following physical activity (Coletti et al., 2005; Haddad, Zaldivar, Cooper, & Adams, 2005). This phenomenon is because infiltrating, inflammatory cells degrade exercise-induced damaged tissues (prior to the regeneration phase) through the release of proteolytic enzymes, cytokines, and cytotoxic mediators (Beckman & Koppenol, 1996; Witko-Sarsat, Rieu, Descamps-Latscha, Lesavre, & Halbwachs-Mecarelli, 2000). Overwhelming, prolonged production of these mediators may harm surrounding healthy tissues (Beckman & Koppenol, 1996; Witko-Sarsat et al., 2000), thereby inhibiting regeneration (Coletti et al., 2005; Haddad et al., 2005), thus negatively impacting exercise-induced tissue adaptations and performance (Smith, 2003b).

2.6.b Systemic Effects

Strenuous exercise (i.e., high intensity with or without prolonged durations) performed on a daily basis has additional systemic effects by directly over-activating the HPA axis (Angeli et al., 2004). Exercise stimulates CRH, which then acts on the pituitary gland, causing it to release ACTH, which then acts on the adrenal cortex causing the hypersecretion of cortisol (Mastorakos et al., 2005).

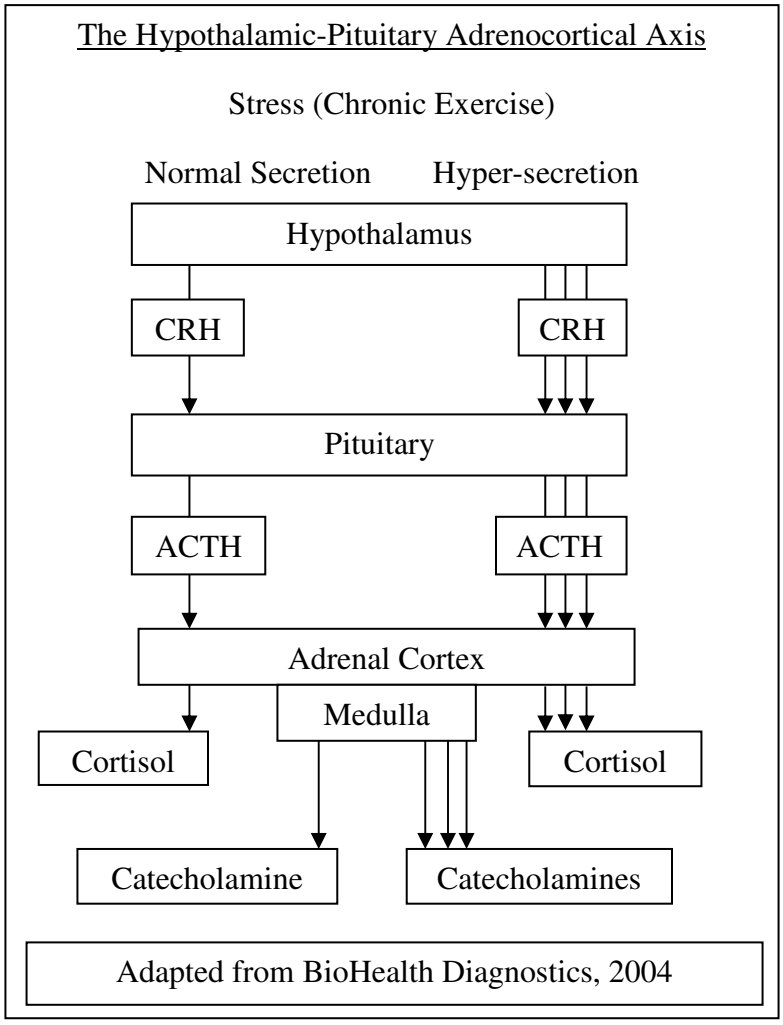

Figure 2: Over-Stimulation of the HPA Axis Induced by Chronic Exercise

Legend

CRH = Corticotropin-Releasing Hormone
ACTH = Adrenocorticotropic Hormone

Exercise stimulates the HPA axis and *chronic exercise* over-stimulates the HPA axis (Angeli et al., 2004). Over-stimulation induces enhanced cortisol release, which has several systemic consequences including: impaired exercise adaptation (Angeli et al., 2004), enhanced risk for upper respiratory tract infections (URTIs; Kakanis et al., 2010; Nieman, 2003), decreased protein synthesis, and reduced testosterone production (Mastorakos et al., 2005).

2.6.b.i. Impaired Muscle Regeneration

Enhanced cortisol secretion impairs the exercise-induced inflammatory response and tissue regeneration, thereby interfering with normal adaptations to physical exercise (Angeli et al., 2004). These effects are because, during strenuous exercise, injured muscle tissues release inflammatory mediators (Malm, 2001); cortisol suppresses the production of these mediators, thereby attenuating the general features of inflammation (Flaster et al., 2007). One of these features include the trafficking of circulating leukocytes (Chrousos, 1995), which are important in the regeneration of muscle tissues (Yin et al., 2013). Healing of muscle tissues, and thus, adapting to exercise, is dependent on the efficiency of inflammatory cell recruitment to the site of muscle damage (Tidball, 2005). Normally, infiltrating neutrophils and macrophages, induced by inflammatory mediators, degrade the damaged tissues, and phagocytose the remaining cellular debris (Lapointe et al., 2002). If the degradation and phagocytosis of muscle cells are hampered, the healing of muscle tissues is also affected (da Silva & VazMacedo, 2011; Mourkioti & Rosenthal, 2005). Furthermore, during inflammation, macrophages release many growth factors, including IGF-1, which is important for initiating the regeneration of new muscle tissues (Huard, Li, & Fu, 2002; Li & Huard, 2002). Therefore, the suppressive effects of cortisol also impair the trafficking of circulating leukocytes, specifically macrophages, into the muscle tissue, also delaying or inhibiting the growth signals required for the regeneration of muscle tissues (Prisk & Huard, 2003).

2.6.b.ii Enhanced Upper Respiratory Tract Infections

Prolonged high-intensity exercise has been shown to increase the athlete's risk for URTIs (Kakanis et al., 2010; Nieman, 2003). It is hypothesized that the immunosuppressive effects induced by the hypersecretion of cortisol can last between 3 to 72 hours (Nieman, 2003).

Because cortisol is a systemic hormone, its immunosuppressive effects are not limited to the inflamed muscle tissue (Flaster et al., 2007; Tsigos & Chrousos, 2002). It is hypothesised that this phenomenon provides opportunity for respiratory viruses to overcome innate defence mechanisms in athletes; leading to enhanced URTI rates (Kakanis et al., 2010; Nieman, 1994; 1997; 2003). This theory, called the Open-Window Theory, was collaboratively coined by personnel involved in the sub-discipline of exercise immunology (Kakanis et al., 2010; Nieman, 2003; Nieman, 1994; Nieman, 1997). Dr. Nieman, one of the pioneers in the development of exercise immunology, depicted the relationship between exercise dose and susceptibility to infections as a J-shaped curve (Nieman, 1997; Shephard, 2010). This model suggests that moderate physical activity may decrease the risk for URTIs, whereas too much exercise could increase the risk (Nieman, 1997).

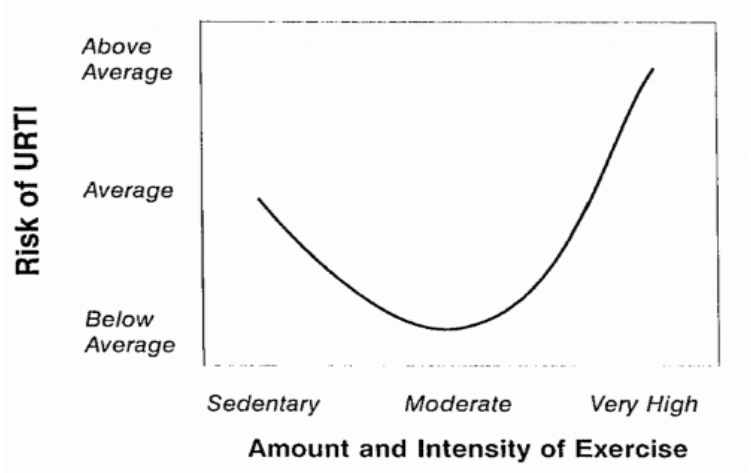

Figure 3: The J-shaped curve depicts that the risk of contracting URTIs may be lowered through moderate exercise; however, may increase by excessive physical activity (Nieman, 1994).

2.6.b.iii Decreased Protein Synthesis

During exercise, both cortisol and catecholamines (epinephrine and norepinephrine) influence the mobilization of energy reserves (Lundberg, 2005) necessary for both brain and

muscle function (Carrasco & Van de Kar, 2003). Catecholamines are synthesized from the amino acid L-Tyrosine, however their synthesis requires the presence of several key enzymes including, tyrosine hydroxylase, which is the rate limiting enzyme of the catecholamine synthetic pathway (Dunkley, Bobrovskaya, Graham, Nagy-Felsobuki, & Dickson, 2004). In the final step of this pathway, norepinephrine is transformed into epinephrine in presence of the N-methyltransferase enzyme (Ziegler, Bao, Kennedy, Joyner, & Enns, 2002). CRH and ACTH help to sustain the presence of tyrosine hydroxylase while, at the same time, cortisol induces the increase in N-methyltransferase; therefore, selectively stimulating epinephrine synthesis (Kvetnansky et al., 1995).

Catecholamines mobilize energy reserves during physical activity by increasing: gluconeogenesis (the synthesis of glucose from non-carbohydrate molecules); lipolysis (the breakdown and release of fatty acids); and protein catabolism (Mastorakos et al., 2005). While exercise output is dependent on energy mobilization, strenuous and chronic exercise, inducing the hypersecretion of cortisol, is believed to induce a prolonged mobilization of energy reserves (Borer, 2003), such that a decrease in protein synthesis for muscle and connective tissues ensues (Giunta, 2008). Furthermore, cortisol reduces amino acid transport into muscles (Borer, 2003) further impairing the regeneration of muscle tissues and adaptation to physical activity, which affect subsequent exercise bouts (Angeli et al., 2004).

2.6.b.iv Reduced Testosterone and Estrogen Production

The Hypothalamic-Pituitary-Gonadal (HPG) Axis (also called the reproductive axis) is directly influenced by the HPA axis (Mastorakos et al., 2005). The HPG axis controls development, reproduction, and aging (Atwood & Bowen, 2011). Gonadotropin-releasing hormone (GnRH) is secreted from the hypothalamus, which acts on the pituitary gland,

producing luteinizing hormone (LH) and follicle-stimulating hormone (FSH),which then act on the gonads producing estrogen and testosterone (Tsigos & Chrousos, 2002). The ovaries mainly produce estrogen; however, this sex steroid is also produced by the adrenal cortex, placenta (during pregnancy), and testes to a lesser degree (Nelson & Bulun, 2001). In men, testosterone is predominantly produced by the testes (Peper, van den Heuvel, Mandl, Hulshoff Pol, & van Honk, 2011), but the ovaries and adrenal cortex produce it in smaller amounts as well (Burger, 2002). Sex steroids are normally secreted during exercise (Brownlee, Moore, & Hackney, 2005; Consitt, Copeland, & Tremblay, 2002); however, as the intensity and duration of exercise increases, with subsequent enhanced activation of the HPA axis, the HPG axis may become suppressed (Nindl et al., 2001). The HPG axis is inhibited by the HPA axis through CRH and cortisol (Tsigos & Chrousos, 2002). CRH inhibits the secretion of GnRH by suppressing the GnRH neurons of the arcuate nucleus of the hypothalamus (Tsigos & Chrousos, 2002). Cortisol, on the other hand, inhibits the HPG axis at all three levels by: 1) suppressing the hypothalamus from secreting GnRH; 2) suppressing the pituitary gland from secreting LH; and 3) suppressing the gonads from secreting estrogen and testosterone (Tsigos & Chrousos, 2002). Furthermore, cortisol causes target tissues of estrogen and testosterone to be resistant or less responsive to these sex steroids (Tsigos & Chrousos, 2002).

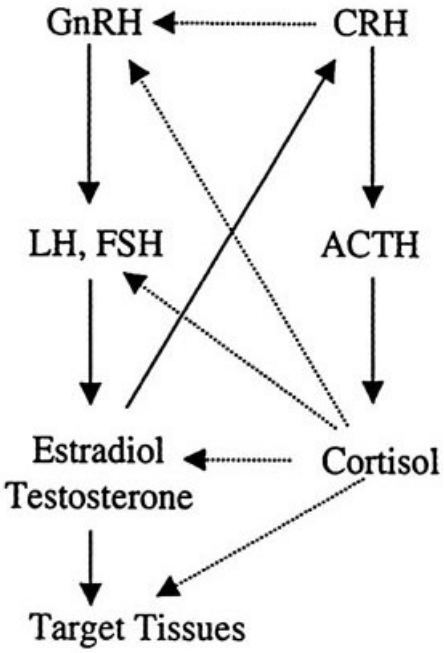

Figure 4: Cortisol Inhibition of the HPG Axis at the Three Levels. The doted arrows signify cortisol inhibition of the HPG axis at all three levels.

Figure from Mastorakos et al., 2005

Legend

GnRH = Gonadotropin-Releasing Hormone
LH = Luteinizing Hormone
FSH = Follicle-Stimulating Hormone
CRH = Corticotropin-Releasing Hormone
ACTH = Adrenocorticotropic Hormone

Importantly, testosterone is involved in the synthesis of skeletal muscle protein, the growth of skeletal muscles, and the maintenance of muscle mass and strength (Vingren et al., 2010). Additionally, testosterone exerts anti-catabolic effects by inhibiting the degradation of protein, and plays a significant role in adaptations to physical exercise (Vingren et al., 2010); that is, the increase in muscle growth and strength following exercise is highly dependent on testosterone (Vingren et al., 2010). In men, decreased testosterone causes a decline in protein synthesis, strength and fat oxidation (Kvorning, Andersen, Brixen, & Madsen, 2006). Decreased

testosterone also results in reduced athletic performance (Halson & Jeukendrup, 2004). The physiological role of testosterone in females is poorly understood (Enea, Boisseau, Fargeas-Gluck, Diaz, & Dugué, 2011). However, an elevation in testosterone levels following a short-term bout of endurance exercise has been reported in females (Consitt et al., 2002), and an association between elevated testosterone levels and increases in muscular strength following training has been observed in women (Consitt et al., 2002). Therefore, the consequence of testosterone secretion inhibition in females is potentially equally detrimental to the normal physiological adaptations of exercise as in males.

Estrogen also plays an important role in the adaptations to exercise (Plowman & Smith, 2008). This sex hormone is important in the formation, resorption, and turnover of bones throughout the lifespan (Plowman & Smith, 2008). Specifically, estrogen assists with the bone changes required by increased physical demand (Mastorakos et al., 2005). Additionally, estrogen is important in the regulation of ovulation in females, both of which can be affected by over-stimulation of the HPA axis (Jabbour, Kelly, Fraser, & Critchley, 2006).

Highly trained athletes are at an increased risk for suppressed gonadal function, caused by over-stimulation of the HPA axis in response to the chronic exercise-induced inflammatory response (Tsigos & Chrousos, 2002). Suppressed HPG axis function results in low levels of sex steroids for both sexes (Mastorakos et al., 2005). In females, decreased sex steroid levels, particularly for estrogen, cause amenorrhea (absence of menstruation), oligomenorrhea (decreased or light menstruation), anovulation (absence of ovulation), decreased bone density, (which may be irreversible) and predisposes athletes to osteopenia and osteoporosis, as well as short- or long-term infertility (Warren & Perlroth, 2001). In males, reduced estrogen can cause

decreased spermatogenesis, decreased bone maintenance (which may lead to osteopenia and osteoporosis (Simpson et al., 2000), and infertility (Hackney, 2008; Simpson et al., 2000).

Overall, exercise-induced, chronic inflammation will directly hinder training adaptations, cause performance decrements, prolonged recovery time, persistent muscle soreness/tenderness, chronic fatigue, depletion of glycogen stores, and decreased levels of macro- and micronutrients through direct and indirect means (Smith, 2003b).

2.7 Summary

A primary purpose of the HPA axis is to maintain homeostasis when an organism is presented with intrinsic or extrinsic stressors (Stratakis & Chrousos, 1995). Therefore, activation of the HPA axis through the exercise-induced inflammatory response also serves to maintain homeostasis (Mastorakos et al., 2005). Homeostasis is challenged by exercise because it is characterized as a physical stress; thus, plasma levels of cortisol are elevated to regulate the immune response (Mastorakos et al., 2005). Without the modulation of the immune response by the HPA axis, the immune system would damage host tissues, increasing one's vulnerability to autoimmune/inflammatory diseases (Stratakis & Chrousos, 1995). Additionally lack of immune modulation would also hinder adaptations to physical activity, and thus, cause a decline in exercise performance. On the other hand, over-activation of the HPA axis in response to the exercise-induced inflammatory response would result in excess secretion of cortisol, which could increase one's vulnerability to infections and/or neoplasias (Stratakis & Chrousos, 1995). Thus, the exercise-induced inflammatory response and the HPA axis must function in balance for optimum health and training results (Stratakis & Chrousos, 1995).

This chapter primarily focused on the advantages and disadvantages of the exercise-induced inflammatory response and the subsequent activation of the HPA axis. To summarize,

exercise-induced inflammation can be beneficial to individuals, but it may also be detrimental. Age has significant impacts on both immune function and underlying inflammatory status (Franceschi et al., 2007; Gomez et al., 2008; Weiskopf et al., 2009), which are discussed next.

Chapter 3: Age Span

3.1 The Aging Process

A clear and congruent definition of aging remains to be elucidated (Balcombe & Sinclair, 2001); nonetheless, aging is typically defined as "the accumulation of damage to somatic cells, leading to cellular dysfunction, and culminates in organ dysfunction and an increased vulnerability to death" (Izaks & Westendorp, 2003 p. 6). According to biologists, aging is a "continuous process that starts at conception and continues until death" (Balcombe & Sinclair, 2001, p. 836). However, the definition of aging is often simplified to "the passage of time from birth onwards" (Balcombe & Sinclair, 2001, p. 837). This definition implies that the number of physical, mental and functional problems, and age-related mortality rates increases with the passage of time; i.e., as individuals age (Balcombe & Sinclair, 2001). During aging, all systems are affected, both directly and indirectly via interaction with other aging systems (Weinert & Timiras, 2003). Cell damage is influenced by a variety of intrinsic and extrinsic environmental factors, and the ability of the body's defence mechanisms to cope with these stressors (Franceschi et al., 2000b; Gomez et al., 2005). Internal environments include products of metabolism, such as damage produced by ROS (Franceschi et al., 2007). Examples of external environmental influences include the cumulative damaging effects of ultra violet rays, gamma radiation, heat, air pollutants, viruses, bacteria, and parasites (Franceschi et al., 2000b; Franceschi et al., 2007). Distinguishing between internal and external environmental causes is challenging, even impractical, because many factors are considered as both internal and external environments (Franceschi et al., 2007). For example, ROS can be produced externally through air pollution (Gurgueira, Lawrence, Coull, Murthy, & González-Flecha, 2002), but may also be generated internally through activation of innate immune inflammatory responses (Cannizzo,

Clement, Sahu, Follo, & Santambrogio, 2011). The effects of extrinsic stressors become more harmful and worrisome than intrinsic stressors in aged individuals (Gomez et al., 2005). As individuals age, extrinsic stressors disrupt the balance between pro- and anti-inflammatory mediators more than intrinsic stressors, causing malfunctions in innate immunity (Gomez et al., 2005).

The body has many anti-stress responses at each hierarchical level, including molecular, cellular, systemic and organismal, to offset the detrimental effects of environmental stressors (Franceschi et al., 2007). Some of the most significant defence mechanisms of the body at each level of hierarchy are: a) molecular level: DNA repair enzymes (poly (ADP-ribosyl) polymerase), antioxidants (superoxide dismutase, catalase), stress proteins (heat shock proteins) (Franceschi et al., 2007; Kirkwood & Franceschi, 1992), and protein and organelle turn-over; b) cellular level: apoptosis and autophagy (self-digestion by a cell and/or digestion of organelles within a cell), phagocytosis of pathogens and damaged cells, cell senescence, and repairing and/or replacing damaged and/or dead cells; c) systemic level: responses initiated by the immune and neuroendocrine systems, and the stress response; and d) organismal level: avoiding or reducing danger and damage through behavioural responses (Franceschi et al., 2007). Relevant to this thesis are the changes to the immune system related to aging.

3.1a Alterations in Immune System Function with Age

Aging is also associated with changes in immune function and influences both the innate and adaptive branches of the immune systems (Gomez et al., 2008; Weiskopf et al., 2009). Overall, the entire immune system becomes dysregulated and dysfunctional with age: this process is termed immunosenescence (Fulop et al., 2012; Salminen et al., 2008; Sansoni et al., 2014). However, innate immunity appears to be better conserved, or upregulated; whereas,

adaptive immunity undergoes more severe age-related alterations (Franceschi, Bonafè, & Valensin, 2000a), with noted decline in functional ability (Weng, 2006). General effects noted for the adaptive immune system are the age-dependent dysregulation in T and B lymphocytes (Agarwal & Busse, 2010; Weiskopf et al., 2009). Specifically, T and B lymphocytes retain the capacity to respond to previously encountered antigens with increasing age (i.e., memory cells); however, their ability to react to novel pathogens is poor (McElhaney & Effros, 2009; Weiskopf et al., 2009). Other adaptive immune changes associated with increasing age are well described in the literature; whereas, the influence of aging on innate immune responses remains unclear (Aw, Silva, & Palmer, 2007; Licastro et al., 2005). Pertinent to this thesis are the innate immune responses and therefore this branch is examined specifically below.

3.1b Innate Immune System Function with Age

Aging influences the number, function and activation of immune cells (Gomez et al., 2008), and affects a variety of cell types, including: developing cells in the bone marrow and thymus; and mature cells in the peripheral blood, organs and tissues (Weiskopf et al., 2009). The physical defence mechanisms of innate immunity, that is, the epithelial barriers of the skin, lungs and gastrointestinal tract, deteriorate with age and decrease in function, which increases host susceptibility to pathogen invasion (Gomez et al., 2005). Furthermore, individual cells of the innate immune system are uniquely affected by the aging process (Fulop et al., 2012; Gomez et al., 2005). We will examine each of these cells separately.

Neutrophils: As we age, the total numbers of circulating neutrophils in the blood are believed to be unaffected; however, neutrophil functions become compromised (Fulop et al., 2004; Wessels, Jansen, Rink, & Uciechowski, 2010). The primary functions include: phagocytosis (the internalization of bacteria or cellular debris), intracellular killing by the

generation of free radicals known as the oxidative or respiratory burst, and chemotaxis (taxis in response to the influence of chemical stimulation; Butcher et al., 2001; Peters et al., 2009; Wessels et al., 2010). Neutrophils play a critical role in antimicrobial immunity via these functions and therefore decline in any of these cells will increase individual infection rates (Dale, Boxer, & Liles, 2008). Under normal circumstances, neutrophils remain in the blood circulation for approximately 6 hours and then die if not recruited to an inflammatory cite (Abbas et al., 2007). Additionally, neutrophils normally receive anti-apoptotic signals during an infection or inflammation (Hajishengallis, 2014) to increase their lifespan, which allow them to assist with pathogenic invasions longer (Hotta et al., 2001), and only undergo apoptosis following microbial activation and removal (Fulop, 1997). However, in individuals 50-60 years of age or greater (Freund, Orjalo, Desprez, & Campisi, 2010), anti-apoptotic signals to neutrophils are reduced during an infection or inflammatory response inducing apoptosis of this cell type prior to clearance of the pathogen (Hajishengallis, 2014). Therefore, this occurrence may cause the infection to persist longer than usual (Lord, Butcher, Killampali, Lascelles, & Salmon, 2001).

Monocytes/Macrophages: Like neutrophils, the total number of monocytes/macrophages does not change with age, but they exhibit age-associated dysfunctions (Aw et al., 2007; Crétel, Veen, Pierres, Bongrand, & Gavazzi, 2010; Panda et al., 2009). Primarily, the chemotactic activity of monocytes/macrophages declines with age, meaning, their ability to recruit inflammatory cells to the site of infection is reduced (Plowden, Renshaw-Hoelscher, Engleman, Katz, & Sambhara, 2004). This phenomenon is linked to alterations in their TLR signalling pathways (Shaw, Panda, Joshi, Qian, Allore, & Montgomery, 2011). Unlike neutrophils (whose chemotactic abilities also weaken with age), the cell surface expression of monocyte/macrophage TLR count decreases with age, which prevents their ability to respond normally to stimulatory

proteins (Agarwal & Busse, 2010; Panda et al., 2009; Renshaw et al., 2002; Shaw, Joshi, Greenwood, Panda, & Lord, 2010). TLR play a critical role in the early innate immune response to invading pathogens by sensing the presence of microorganisms, via common protein expression (Abbas et al., 2007). Further studies are needed to confirm this notion (Agarwal & Busse, 2010; Panda et al., 2009; Renshaw et al., 2002; Shaw et al., 2010).

Conversely, studies performed *in vitro* using human cells have shown that the general production and secretion of pro-inflammatory cytokines, notably IL-6, are increased from monocytes/macrophages with age (O'Mahony et al., 1998; Roubenoff et al., 1998; Sadeghi, Schnelle, Thomas, Nishaniana, & Fahey, 1999). IL-6, along with other cytokines, stimulates the maturation and differentiation of B lymphocytes, which leads to specific antibody production (Abbas et al., 2007; Sadeghi et al., 1999). This cytokine is also a pro-inflammatory mediator (Akira, Hirano, Taga, & Kishimoto, 1990), and stimulates the production of CRP; an acute-phase protein produced by the liver, as previously discussed (Abbas et al., 2007). CRP is involved in the recognition of pathogens and tissue injuries, and thus, the recruitment of phagocytic cells as a mean to mediate their elimination (Volanakis, 2001). The increase in IL-6, nevertheless, may be involved in the pathogenesis of age-related diseases (Singh & Newman, 2011), which will be discussed further.

In a literature review conducted by Gomez et al. (2008), a reduction in the ability of monocytes/macrophages to perform phagocytosis and intracellular killing with the generation of free radicals was reported. A study conducted by Swift, Burns, Gray, and DiPietro (2001) compared the phagocytic capacity between young and aged mice, and showed that aged mice had a significant decrease in their phagocytic ability compared to young mice. Alvarez & Santa María (1996) examined the capacity of aged human derived monocytes/macrophages to perform

intracellular killing with the generation of free radicals. The researchers found that aged monocytes/macrophages had a reduced ability to perform this function (Alvarez & Santa María, 1996). As with neutrophils described above, an inability to effectively eradicate invading pathogens via these primary mechanisms increases the risk of succumbing to more frequent and prolonged infections (Gomez et al., 2008).

NK Cells: Unlike neutrophils and monocytes/macrophages, studies conducted with healthy populations of elderly people aged 65 years or greater found that the total number of NK cells increases with age (Borrego et al., 1999; Krishnaraj, 1997; Ligthart, Schuit, & Hijmans, 1989; Sansoni et al., 1993). This increase is hypothesized to be a coping mechanism counterbalancing the age-related declines in immunity described above (Vallejo et al., 2011). Additionally, it has been shown that the cytotoxicity of NK cells is not lost in *healthy* (regarded as "preserved health, quality of life and independence, and physical, social and mental wellness; Peel, Bartlett, & McClure, 2004, p. 115), aging individuals (Borrego et al., 1999; Ligthart et al., 1989; Sansoni et al., 1993), contributing to longevity (Almeida-Oliveira et al., 2011; Le Garff-Tavernier et al., 2010). Nevertheless, the degree of cytotoxicity of NK cells in the general elderly population has been shown to decline; also increasing individual susceptibility to developing infectious diseases (Ogata et al., 2001). NK cell assessment of function is difficult to interpret, because the effects of aging on the cytotoxic function of NK cells depend on whether they are assessed as a group or individually (Fulop et al., 2012). Specifically, the cytotoxic activity of each NK cell may decline with age; however, overall function may remain unaffected, or even increase, when NK cells are considered as a group, due to the age-related increase in total cell counts of this type of innate cell (Fulop et al., 2012). The age-related increase in NK cell count,

discussed above, may also be a mechanism accounting for the decrease in per-cell cytotoxic function (Mocchegiani & Malavolta, 2004).

Finally, one function of NK cells is to recognize (Zhang et al., 2007) and eliminate virus-infector or tumour cells (Gayoso et al., 2011), and may self-activate without additional activation signals when in contact with diseased cells (Abbas et al., 2007). Nevertheless, NK cells may also be activated by cytokines secreted by other immune cells resulting in their proliferation, enhanced cytotoxic function, and the production and secretion of cytokines and chemokines (Gayoso et al., 2011). T cells, an adaptive immune cell, may stimulate the proliferation and cytotoxic activity of NK cells through the secretion of IL-2 (Vivier, Tomasello, Baratin, Walzer, & Ugolini, 2008). However, the ability of NK cells to proliferate in response to the IL-2 cytokine decreases with age (Borrego et al., 1999). Decreased proliferation of NK cells may increase the frequency of infectious diseases, and could result in prolonged illness (Chandra, 1992). Additionally the capacity of NK cells to generate several cytokines and chemokines has been shown to decline with increasing age (Mocchegiani, Giacconi, Cipriano, & Malavolta, 2009). Cytokines of the innate immune system have numerous functions, such as recruiting and activating leukocytes and enhancing their effector functions (Abbas et al., 2007), and mediating communication between immune cells (Abbas et al., 2007). Chemokines are responsible for stimulating the movement of leukocytes and regulating leukocyte trafficking (Abbas et al., 2007). Thus, the decreased capacity of NK cells to produce some cytokines and chemokines reduces the ability of the immune system to deal with pathogens (Gayoso et al., 2011).

Importantly, the production of IFN-γ by NK cells appears to be unaffected by the aging process (Le Garff-Tavernier et al., 2010). IFN-γ is a cytokine involved in the activation of macrophages during immune responses (Abbas et al., 2007); therefore, the capacity of the

immune system to defend against pathogen invasions is somewhat maintained (Le Garff-Tavernier et al., 2010).

3.1c Inflammaging

Inflammaging is a term coined by Franceschi et al. in 2000b, and is defined as aging associated with a mild chronic pro-inflammatory state. Ironically, inflammation and immunodeficiency exist simultaneously during the aging process, which is a phenomenon left unexplained; only speculated upon (Giunta, 2008). Inflammaging is characterized by increased activation of the NF-κB signalling cascade in innate immune cells; the primary pathway regulating inflammation, via elevated circulating levels of pro-inflammatory mediators, notably: IL-1, IL-6 and TNF-α, and acute-phase proteins, including: CRP (Franceschi et al., 2000b).

Researchers have been notably interested in IL-1, IL-6, TNF-α, and CRP, as they are "the inflammatory markers most consistently associated with age-related chronic diseases and disability" (Singh & Newman, 2011, p. 1). As individuals age, the levels of these pro-inflammatory mediators increase in healthy individuals, individuals with pathological conditions, and healthy centenarians (Franceschi et al., 2000b). Noticeable increases appear between the ages of 50-60 years, and generally remain low or even untraceable in young individuals (Ershler & Keller, 2000; Fagiolo et al., 1993; Shaw et al., 2010; Singh & Newman, 2011), except during times of physiologic stress (Singh & Newman, 2011). The level of increase in pro-inflammatory markers in aging individuals with pathological conditions is much higher than those who are healthy (Singh & Newman, 2011) defined as "those who have the better capacity to adapt to damaging agents and in particular to immunological stressors" (Franceschi et al., 2000c, p. 885). Thus, assumptions can be made that high levels of pro-inflammatory mediators are associated with morbidity and/or mortality, especially in extremely aged individuals, such as centenarians

(Franceschi et al., 2000b). Increases in these pro-inflammatory markers, especially high levels, are associated with diseases and physical and cognitive disabilities (Chung et al.,2009; Sikora, Scapagnini, & Barbagallo, 2010; Singh & Newman, 2011; Yu & Chung, 2006). Therefore, these pro-inflammatory mediators may be used as predictors of age-related conditions (Singh & Newman, 2011), such as cardiovascular diseases (Bruunsgaard, Skinhoj, Pedersen, Schroll, & Pedersen, 2000), cancer (Aggarwal, Shishodia, Sandur, Pandey, & Sethi, 2006), diabetes (DeRekeneire et al., 2006), cognitive declines (dementia, Alzheimer's disease; McGeer & McGeer, 2004), frailty, sarcopenia (decline in muscle mass and strength; Jensen, 2008), and many others (Singh & Newman, 2011).

3.2 Specific Mechanisms Contributing to the Decline in Immunity and Inflammaging

Among the various intrinsic and extrinsic environmental factors contributing to cell damage overtime, and thus, the decline in immunity and inflammaging, an age-related redox imbalance may be one of the main culprits responsible for the chronic up-regulation of pro-inflammatory mediators during aging (Chung et al., 2009). Many theories have been proposed over the past several decades to explain the cause and mechanisms of aging, and hence, inflammaging (Dice, 1993); however, the oxidative stress hypothesis is the current premise that is widely accepted (Chung et al., 2009; Sohal, Mockett, & Orr, 2002; Yu & Yang, 1996). This theory is a modification and an advancement of the free radical theory of aging, which was proposed by Denham Harman in the 1950's (Pérez et al., 2009) and became credible between 1968-1969 (Backman & Ames, 1998; Buettner, 2011). The free radical theory of aging states that oxidative damage caused by an excess production of ROS by mitochondria, due to normal metabolism, is linked to aging and associated degenerative diseases (Harman, 2006; Pamplona & Barja, 2007; Trifunovic et al., 2004). This theory also suggests that the speed at which

mitochondria accumulate oxidative damage, mainly mitochondrial DNA, influences the lifespan of organisms (Harman, 2006). Nonetheless, the oxidative stress hypothesis suggests that an excess accumulation of other oxidants, such as RNS for example, also causes oxidative damage; therefore, influences aging and associated degenerative diseases (Chung et al., 2009). Thus, the oxidative stress hypothesis implies that oxidative stress is not solely instigated by an over-production of ROS, but by other oxidants as well, referred to as reactive species (Chung et al., 2009). The redox balance of organisms counters these effects and is dependent on the defence mechanisms of anti-oxidants (Chung et al., 2009), which are discussed further below. Unlike the free radical theory of aging, the crucial role of anti-oxidants is stressed by the oxidative stress hypothesis (Chung et al., 2009), discussed below.

Molecules that contain a single unpaired electron or two unpaired electrons in their outer electron orbital are free radical species (Cannizzo et al., 2011), or reactive species (Chung et al., 2009). The following are examples: free radicals having one unpaired electron in their outer orbital include hydrogen ($H^{\cdot}$), nitric oxide ($NO^{\cdot}$), hydroxyl radical ($^{\cdot}OH$), peroxyl radicals (RO_2), alkoxyl radicals ($RO^{\cdot}$) and transition metals (copper and iron); and those containing two unpaired electrons in their outer orbital consist of diatomic molecular oxygen (O_2) and its derivative known as superoxide ($O^{\cdot-}_2$) (Cannizzo et al., 2011). The degree of reactivity and half-life of each free radical vary; nonetheless, the majority are very unstable and oxidize biomolecules, such as proteins, carbohydrates, lipids and nucleic acids, inducing oxidative damage (Cannizzo et al., 2011;Valko, Rhodes, Moncol, Izakovic, & Mazur, 2006). Although detrimental in high concentrations, some reactive species are required in low concentrations for normal physiological processes (Allen & Bayraktutan, 2009). For example, endogenous ROS are involved in cell signalling, induction of mitogenesis, immune defence, apoptosis, cellular

senescence, and the breakdown of toxic compounds (Allen & Bayraktutan, 2009). Furthermore, many responses induced by ROS serve to protect cells against oxidative damage and restore or sustain redox homeostasis (Dröge, 2002; Valko et al., 2007).

The generation of free radicals comes from three main sources, including: oxidative metabolism; oxidative burst of immune cells; and the environment (Cannizzo et al., 2011). Nevertheless, both the free radical theory of aging and the oxidative stress hypothesis are in agreement that oxidative metabolism is the predominant factor contributing to oxidative stress, and thus, the aging process (Harman, 2006; Pamplona & Barja, 2007; Sohal et al., 2002; Trifunovic et al., 2004).

Normal cellular functioning is dependent on mitochondria as this organelle executes a variety of functions, such as producing ATP (chemical energy), oxidizing fatty acids, metabolising amino acids and lipids, regulating apoptosis (Desler, Marcker, Singh, & Rasmussen, 2011), and maintaining redox homeostasis (James et al., 2009). Mitochondria, particularly mitochondrial DNA, are substantially susceptible to redox stress because they are the primary source of free radicals, which are generated during cellular respiration (Cadenas & Davies, 2000). Specifically, as electrons are being transported back and forth in the mitochondrial respiratory chain, reactive species are being generated (Cannizzo et al., 2011). Therefore, the function of cells and organs becomes dysregulated leading to the decline of the entire system, which is characterized as aging and the development of degenerative diseases (Valko et al., 2007).

The oxidative, or respiratory burst, of innate immune cells remains dormant in resting cells, and is activated upon the invasion of pathogens (Dale et al., 2008). Once this antimicrobial pathway is activated, oxidizing agents are released to eradicate the invading pathogen (Ciz et al.,

2012). The ability of innate immune cells to produce oxidizing agents decreases with age; however, their overall oxidative burst activity increases resulting from the increased rate of pathological conditions and tissue damage (Agarwal & Busse, 2012).

Environmental stressors such as ultraviolet light, ionizing radiations, dietary factors, cigarette smoke, alcohol, and some medications (Valacchi et al., 2012) often generate free radical species (Burke & Wei, 2009; Franceschi et al., 2007; Valacchi et al., 2012). Other sources of free radicals include air pollutants; for example, diesel fuel exhaust, halogenated hydrocarbons, heavy metals and ozone (Valacchi et al., 2012).

Organisms are protected against oxidative stress through maintenance of redox homeostasis by anti-oxidants, and are defined as "any substance that delays, prevents or removes oxidative damage to a target molecule" (Gutteridge & Halliwell, 2010, p. 561). Anti-oxidant defences may be enzymatic or non-enzymatic (Chung et al., 2009); for example, enzymatic anti-oxidants include superoxide dismutase, glutathione peroxidase and catalase (Gutteridge & Halliwell, 2010), and non-enzymatic anti-oxidants consist of vitamin C, E and A, β-carotene and uric acid (Hamid, Aiyelaagbe, Usman, Ameen, & Lawal, 2010). The most potent and abundant anti-oxidant, however, is glutathione peroxidase (Chung et al., 2009). Overtime, reactive species accumulate, and anti-oxidant levels decrease and their defence mechanisms against oxidants weaken (Chung et al., 2011). These phenomena disrupt redox homeostasis inducing a redox imbalance, which leads to over-oxidation, and therefore, influences the aging process and inflammaging (Chung et al., 2009). Thus, redox homeostasis is predominantly dependent on the balance between oxidants and anti-oxidants (Chung et al., 2011).

Oxidants may induce the inflammatory response directly (Chung et al., 2009) or indirectly (Jaeschke, 2011). 1) Directly: Oxidants include one of many stimuli for initiating pro-

inflammatory signalling pathways and transcription factors, and the resulting activation of genes encoding pro-inflammatory mediators (Chung et al., 2009; Kyriakis & Avruch, 2010). Because free radicals are endotoxins, they are considered as pathogen-associated molecular patterns (PAMPs) thus they bind to PRRs located on immune cells, which activates inflammation (Jaeschke, 2011).

Oxidant-induced activation of the immune system is normally short-lived as the reaction and levels of reactive species are modulated by anti-oxidants (Yu & Chung, 2006). However, it is believed that the decline in an organism's ability to control levels of reactive species and maintain redox homeostasis results in chronic inflammation, and in turn, tissue damage, aging, and age-related diseases (Yu & Chung, 2006), such as neurodegenerative and cardiovascular diseases, osteoarthritis, rheumatoid arthritis, atherosclerosis (McGeer & McGeer, 2004), Alzheimer's disease, diabetes (Candore et al., 2009), insulin resistance (Bruunsgaard, 2002), infections, and cancer (Agarwal & Busse, 2010). 2) Indirectly: The accumulation of oxidative damage to biomolecules results in a surplus of DAMPs; these also bind to PRRs of innate immune cells similarly inducing chronic inflammation (Jaeschke, 2011). Thus, further tissue damage occurs, contributing to aging and its associated degenerative diseases (Jaeschke, 2011), such as Alzheimer's disease, for example (McGeer & McGeer, 2004).

This chronic pro-inflammatory state eventually damages host tissues as well creating further inflammation and more tissue damage; hence, a vicious cycle occurs (Chung et al., 2009). Additionally, an age-related decline in anti-oxidant levels occurs (Lavrovsky, Chatterjee, Clark, & Roy, 2000) shifting the cellular redox state and inducing irreversible changes in the structure and function of biomolecules (Sohal & Orr, 2012). Again, this cellular redox imbalance supports a chronic pro-inflammatory state, with a recurrent need to scavenge and remove these damaged

cell structures and proteins (Cannizzo et al., 2011). Therefore, the chronic pro-inflammatory state associated with aging contributes largely to age-related diseases (Candore et al., 2010; Chung et al., 2009; De Martinis, Franceschi, Mont, & Ginald, 2005).

3.3 How the Decline in Immunity Affects Aging Individuals/Elders

The age-dependent dysfunction in immunity is correlated with a weakened and slowed response to infections in the elderly (Gomez et al., 2005; Plackett, Boehmer, Faunce, & Kovacs, 2004). Consequently, the prevalence, rate, and severity of infectious diseases, such as respiratory tract infections for example, are increased (Plackett et al., 2004; Weiskopf et al., 2009). Due to the inability of the adaptive immune system to respond to novel proteins, the effectiveness of vaccination is weakened in the elderly (Gomez et al., 2005; Weiskopf et al., 2009), while their risk of contracting more dangerous and persisting infections is greater (Plackett et al., 2004). Evidence supporting this circumstance comes from several areas of research. First, the occurrence of respiratory tract infections is higher in elderly people and caused by pathogens not typically responsible for respiratory infections (Gotfried, 2001; Ruiz et al., 1999) because host resistance to infectious agents declines with age (Yoshikawa, 2000). Second, susceptibility to staphylococcus aureus infections and tetanus are higher among older than younger individuals (Laupland, Church, Mucenski, Sutherland, & Davies, 2003; Pascual, McGinley, Zanardi, Cortese, & Murphy, 2003). Additionally, elders are more vulnerable to infections and sepsis following an injury, and to common age-related diseases (Gomez et al., 2008; Plackett et al., 2004), such as neurodegenerative and cardiovascular diseases, osteoarthritis, rheumatoid arthritis, atherosclerosis (McGeer & McGeer, 2004), Alzheimer's disease, diabetes (Candore et al., 2009), insulin resistance (Bruunsgaard, 2002), and cancer (Agarwal & Busse, 2010). Other infections common among elders include urinary tract infections, lower respiratory tract

infections, skin and soft tissue infections, intra-abdominal infections (cholecystitis, diverticulitis, appendicitis, abscesses), infective endocarditis, bacterial meningitis, tuberculosis, and herpes zoster (Yoshikawa, 2000). The elderly are more susceptible to morbidity and/or mortality resulting from these infections than younger adults with the same disease due to the age-related decline in immunity (Yoshikawa, 2000).

3.4 Anti-Inflammaging

Inflammaging is postulated to be counterbalanced by a mechanism termed anti-inflammaging, which is characterized by elevated levels of cortisol (Franceschi et al., 2007; Giunta, 2008) and other anti-inflammatory mediators, such as soluble IL-1 receptor antagonist (sIL-1Rα), soluble TNF receptor (Goto, 2008; Salminen et al., 2008), IL-4, IL-10, and IL-13 (Lio et al., 2003). Anti-inflammaging is indeed the long-term activation of the HPA axis in response to elevated levels of pro-inflammatory cytokines, mainly IL-1, IL-6 and TNF-α, also correlated with the aging process as described above (Giunta, 2008). It is important to understand that anti-inflammaging, or the persistent activation of the HPA axis, does not simply inhibit inflammaging (Giunta, 2008). Rather, HPA axis activation during aging generally serves to remodel and regulate the immune system to maintain homeostasis, and prevent it from overacting, thus reducing additional tissue damage and injuries (Giunta, 2008). Furthermore, anti-inflammaging is designed to provide robustness against the detrimental effects of inflammaging and may confer longevity (Franceschi et al., 2007). However, although this mechanism is designed to offset inflammaging and ensure robustness, the chronic secretion of cortisol may also have detrimental effects (Baylis, Bartlett, Patel, & Roberts, 2013; Giunta, 2008). The long-term elevated levels of cortisol may partly explain the paradox of inflammaging and immunodeficiency existing concurrently during the aging process (Giunta, 2008), and the increased rate of infections in

elders (Agarwal & Busse, 2010). Anti-inflammaging is also correlated with age-related frailty through cortisol-induced catabolism of many tissues (liver gluconeogenesis, muscle protein catabolism, lipolysis of adipose tissues and bone resorption; Giunta, 2008).

3.5 Sarcopenia

Both cortisol (anti-inflammaging) and inflammatory cytokines (inflammaging) are contributing factors of an age-related process termed sarcopenia (Beyer, Mets, & Bautmans, 2012; Licastro et al., 2005; Moulias, Meaume, & Raynaud-Simon, 1999). Sarcopenia is the degenerative loss of skeletal muscle mass and strength associated with aging, (0.5-1% loss per year after the age of 25), and is a component of frailty syndrome in the elderly (Beyer et al., 2012; Licastro et al., 2005; Moulias et al., 1999). Protein lysis of skeletal muscles is stimulated by inflammatory cytokines and stress hormones (Moulias et al., 1999). Furthermore, oxidative stress damages muscle DNA, protein and lipids, which is also implicated in the deterioration and loss of muscle fibres, and the decline in muscle function (Dirks & Leeuwenburgh, 2006). During aging, deletions and mutations within mitochondrial DNA of skeletal muscles induces weakening of mitochondrial function, promoting additional production of internal free radicals and lipid peroxidation activity (Dirks & Leeuwenburgh, 2006). Therefore, muscle tissues also engage in a chronic pro-inflammatory state during the aging process (Schaap, Pluijm, Deeg, &Visser, 2006). Sarcopenia is caused by multiple age-related factors, including loss of α-motor neurons and their input, decreased synthesis of anabolic hormones, and resistance to stimuli of anabolic hormones (Greenlund & Nair, 2003). The number of satellite cells residing within skeletal muscle tissues decline during aging, which also influences sarcopenia since satellite cells are precursors to skeletal muscle cells (Le Grand & Rudnicki, 2007). Additionally, unfavourable lifestyle choices, such as reduced dietary protein consumption and physical inactivity, contribute

to sarcopenia (Jensen, 2008). Approximately half of the skeletal cell mass is made up of muscle tissue; hence, the aging of the muscular system and the chronic pro-inflammatory state within muscles are significant concerns because the loss of muscle fibres is a predominant contributor to frailty observed during aging (Welle, 2003). Furthermore, sarcopenia causes deficiencies in nutritional reserves, such as protein and glycogen, through insulin resistance; which can also inadvertently weaken immune responses (Moulias et al., 1999; Roubenoff, 2003) since immune cells rely on glycogen as a fuel source and protein for exerting certain functions, such as producing cytokines for example (Gleeson & Bishop, 2000). Insulin resistance in skeletal muscles may be caused by inflammation itself through inhibition of insulin-signalling cascade (de Luca & Olefsky, 2008). TNF-α, in particular, induces insulin resistance by impairing insulin signalling (Peppa, Koliaki, Nikolopoulos, & Raptis, 2010). Other detrimental effects of sarcopenia include mobility loss, increased risk of falls, equilibrium disorders, and physical disability (Moulias et al., 1999). The rate of muscle mass loss in individuals past the age of 50 is 1% to 2% per year (Dirks & Leeuwenburgh, 2006).

The age-related decrease in muscle mass and strength is accompanied with an increase in fat mass, particularly visceral fat, which may lead to sarcopenic obesity; defined as the combination of sarcopenia and obesity (Kohara, 2014). This condition is common among elders, and is concerning because sarcopenic obesity is associated with the risk of developing diseases, including cardiovascular and gallbladder diseases, atherosclerosis, type II diabetes, hypertension, dyslipidemia, strokes, osteoarthritis, many cancers, respiratory problems, and sleep apnea (National Heart, Lung, and Blood Institute, 1998), and therapeutic interventions are scarce in the elderly population (Prado, Wells, Smith, Stephan, & Siervo, 2012). The interaction of many factors, such as endocrine, vascular and immunological factors, and lifestyle, influence

sarcopenic obesity; however, its origin is very complex (Warland, Guillet, Salles, Cano, & Boirie, 2011; Zamboni, Mazzali, Fantin, Rossi, & Di Francesco, 2008). Adipose tissue, particularly visceral fat, contributes to the production of pro-inflammatory cytokines, which is a causative factor in the degree of existing systemic inflammation (Fried, Bunkin, & Greenberg, 1998; Harkins, 2004). In addition, macrophages are abundant among the extracellular space of adipose tissues of obese individuals; thus, they have an overall surplus of macrophages (Fried et al., 1998; Harkins, 2004). This phenomenon further contributes to higher levels of pro-inflammatory mediators in the elderly population, resulting in a high pro-inflammatory status (Fried et al., 1998; Harkins, 2004).

3.6 Why Do Some Individuals Age Successfully, and Others Do Not?

'Successful ageing,' refers to the physical, mental and social well-being in older age (Peel et al., 2004). People 50 years of age or greater in general, have a higher pro-inflammatory status than younger individuals (Freund et al., 2010). People who appear to age successfully, for example, healthy centenarians, appear to have lower levels of pro-inflammatory mediators in their plasma (Freund et al., 2010). The balance between pro- and anti-inflammatory factors, or inflammaging and anti-inflammaging, appears to be a strong determinant of health status for aging individuals (Franceschi et al., 2007) and these networks are balanced in individuals who experience healthy aging and longevity (Franceschi et al., 2007). Likewise, those who experience frailty, age-related pathologies, and a shortened lifespan have an imbalance between pro- and anti-inflammatory factors, and inefficient anti-inflammatory mechanisms to counteract inflammatory responses during the aging process (Capri et al., 2008; Franceschi et al., 2007).

This balance between pro- and anti-inflammatory networks is affected by many factors such as genetics (Candore, Caruso, & Colonna-Romano, 2010; Lio et al., 2003), chronic

exposure to antigens from internal and external environments (De Martinis et al., 2005; Franceschi et al., 2007), and lifestyle (Woods, Wilund, Martin, & Kistler, 2012). Successful aging and longevity is often associated with genetic variants encoding anti-inflammatory responses that are resilient and effective (Candore et al., 2006; Lio et al., 2003; Vasto et al., 2009); healthy centenarians are considered "a model of successful-aging" (Candore et al., 2010, p. 567). People thought to age successfully tend to display genotypes capable of completely neutralizing inflammatory responses instigated by the chronic exposure to internal and external damaging agents (Capri et al., 2008). Nonetheless, unsuccessful aging, characterized by age-related diseases, disability, and early mortality, is typically related to pro-inflammatory genotypes (Candore et al., 2006; Vasto et al., 2009). However, healthy aging and longevity are not influenced by genetics alone, but by interactions between genetics, environmental factors (Capri et al., 2008; Rando, 2013), and chance (Capri et al., 2008). Examples of environmental factors include climate, geographic location, cultural norms, social networks, social support and support from family and friends, and working, housing and economic conditions (Capri et al., 2008).

Antigenic loads, from internal and external environments, are inescapable; however, as previously mentioned, are counteracted and neutralized by various mechanisms of the body (Franceschi et al., 2008). These defence mechanisms weaken during the aging process, which disrupts the balance between the generation and elimination of damaging agents where antigenic loads supersede counteraction, neutralization, and/or elimination; thereby, increases inflammatory responses (Chung et al., 2011). This phenomenon may result in unsuccessful aging and early mortality (Chung et al., 2011). Nonetheless, depending on a variety of factors

(genetics, environment, and chance), an organism may adapt well to the aging process, and thus, confer healthy aging and longevity (Capri et al., 2008; Franceschi et al., 2008).

Examples of lifestyle factors that may influence the balance between inflammaging and anti-inflammaging include diet, exercise (Woods et al., 2012), smoking (MacNee, 2011), and alcohol consumption (Wang, Kakhari, & Jung, 2010).

Hence, as the damage to an organism's cells and tissues continues to accumulate, the risk of age-related diseases and mortality increases proportionately (Rattan, 2008; Troen, 2003). However, the outcome of the aging process is vastly influenced by the balance between pro- and anti-inflammatory mediators (Candore et al., 2010; Salminen, Kaarniranta, & Kauppinen, 2012; Giunta, 2008), which is affected by interactions between genetics (Candore et al., 2010; Lio et al., 2003), environmental factors (De Martinis et al., 2005; Franceschi et al., 2007), lifestyle (Woods et al., 2012), and chance (Capri et al., 2008). The outcome of the aging process may either lead to successful healthy aging and longevity, or frailty, age-related diseases, and a shorten lifespan (Salminen et al., 2012).

In this chapter, a thorough description of the aging process was provided with emphasis placed on the innate immune system. The factors contributing to healthy aging and age-related diseases were also discussed. The following chapter addresses the most significant question concerning this paper: Does inflammation serve a useful purpose for exercise?

Chapter 4: Does Inflammation Serve a Useful Purpose for Exercise?

In summary, the exercise-induced inflammatory response serves a useful purpose for exercise for the following reasons:

a) Inflammation instigated by exercise is essential for performing physical activity optimally through activation of the HPA axis, a.k.a. the stress response. The HPA axis induces physiological changes that are required to respond to the demands of exercise since physical activity is characterized as a physical stressor to the body (Lundberg, 2005). The physiological changes stimulated by the HPA axis, through catecholamines, include heightening arousal, accelerating motor reflexes, increasing alertness, attention, and cognitive function, decreasing appetite and sexual arousal, and increasing pain tolerance (Chrousos, 1995). Additionally, activation of the stress response results in increased heart rate and blood flow; thus, increased oxygen delivery to the exercising muscles (Stratakis & Chrousos, 1995). Without these physiological changes, individuals would be unable to cope with the stress imposed by exercise and exert physical activity at an optimum level.

b) Through the stimulation of catecholamines, cortisol, and GH, the exercise-induced inflammatory response is required for the mobilization of stored fuel into the bloodstream to support muscular contraction and maintain blood glucose levels. These mediators stimulate the mobilization of fuel stored in adipose, liver, and skeletal muscle tissues by binding to receptors located on these cells (Plowman & Smith, 2008). The mobilization of fuel is also directly influenced by inflammation through the secretion of IL-6 (Petersen & Pedersen, 2005). IL-6 binds to adipose tissues stimulating lipolysis and oxidation of fatty acids (Petersen & Pedersen, 2005). The execution of physical activity would not be possible without the stimulation of

catecholamines, cortisol, and GH induced by inflammation during exercise since the lack of fuel would not support muscular contraction.

c) The exercise-induced inflammatory response is crucial for inhibiting the storage of fuel while simultaneously promoting the breakdown of energy by stimulating the secretion of catecholamines. Catecholamines concurrently influence the action of insulin and glucagon where insulin is suppressed and glucagon is secreted (Borer, 2003; Plowman & Smith, 2008); thus, inhibiting the storage of fuel and stimulating the breakdown of substrates, respectively (Fox, 2009). Without the simultaneous suppression of insulin and release of glucagon, the exercising individual would not have sufficient energy to perform optimally.

d) Activation of the HPA axis caused by the exercise-induced inflammatory response is critical for maintaining homeostasis during and following physical activity. Exercise and the exercise-induced inflammatory response are characterized as a physical stress to the human body; therefore, disrupts homeostasis (Stratakis & Chrousos, 1995). As a result, the stress response activates the release of cortisol and other anti-inflammatory mediators to reinstate homeostasis through modulation of the immune response (Mastorakos et al., 2005). Without activation of the HPA axis instigated by the exercise-induced inflammatory response, the immune system would be overactive. The hyperactivity of the inflammatory response would cause excess damage to host tissues increasing the risk for autoimmune/inflammatory diseases (Stratakis & Chrousos, 1995). Additionally, the healing process of skeletal muscles following physical activity would be hindered; thus, decreasing adaptation to exercise and affecting subsequent exercise performance.

e) The exercise-induced inflammatory response is essential for repairing microtrauma to skeletal muscles caused by physical activity. Once infiltrated into damaged muscle tissues,

immune cells mediate and coordinate the repair of injured skeletal muscle cells through various mechanisms (Tidball & Villalta, 2010). The immune response may directly or indirectly influence the repair of skeletal muscle tissues by releasing molecules (Tidball & Villalta, 2010) or influencing other systems of the body (Nehlsen-Cannarella et al., 1997; Nieman et al., 1998), as previously discussed. The immune response may also stimulate the repair of exercise-induced damaged muscle cells by stimulating the activation and proliferation of satellite cells (Tidball & Villalta, 2010; Yin et al., 2013). Without the infiltration of immune cells into damaged skeletal muscle tissues, the regenerative process of injured muscle cells would be delayed, or not take place at all. Therefore, adaptation to physical activity and subsequent exercise performance would be compromised.

f) Mediators of the exercise-induced inflammatory response as well as those of the HPA axis may confer health benefits (Handschin & Spiegelman, 2008). These benefits include reducing the level of systemic inflammation and chronic inflammation associated with inflammatory diseases as long as physical activity is undertaken regularly (Handschin & Spiegelman, 2008). Regular exercise entails accumulating "at least 150 minutes of aerobic physical activity per week, in bouts of 10 minutes or more" (Tremblay et al., 2011, p. 40).

However, the exercise-induced inflammatory response and the subsequent activation of the HPA axis become detrimental to an individual when in excess. An inflammatory response is instigated by acute bouts of exercise followed by the short-term immunosuppressive effects of the HPA axis (Gleeson, 2007). Depending on the intensity and duration of the exercise bout, this temporary immunosuppression typically lasts approximately 3 to 72 hours following physical activity (Nieman, 2003). However, the exercise-induced inflammatory response and the immunosuppressive effects of the HPA axis may last for days depending on the intensity and

duration of the exercise bout as well as the length of the recovery time, i.e., chronic activity, chronically activates the HPA axis (Gleeson, 2007). Furthermore, as previously mentioned, the magnitude of the exercise-induced inflammatory response also depends on the intensity and duration of the exercise bout (Gleeson, 2007).

The literature suggests that the exercise-induced inflammatory response and the subsequent activation of the HPA axis have detrimental consequences when physical activity is prolonged (1-3 hours), performed at moderate to high intensity (equal to or greater than 55% VO_{2max}), and conducted without the ingestion of food (Gleeson, 2007). The data, which were previously discussed above, showed that high-intensity exercise induces immune suppressive effects while moderate-intensity training does not (Plowman & Smith, 2008). However, some researcher will say that moderate- to high-intensity physical activity may cause detrimental effects (Gleeson, 2007; Nieman, 2003), which seems to be a debate in the literature.

Although an over active immune system and continuous activation of the HPA axis have many harmful effects, the greater concern is the immunosuppressive effects of the HPA axis as this phenomenon increases the risk for URTIs (Gleeson, 2007; Plowman & Smith, 2008). The immune system remains dysfunctional for an extended period of time (longer than 3-72 hours post-exercise) in circumstances where exercise bouts are prolonged and intensive for one week or more (Gleeson, 2007). Because the increase in cortisol levels is only evident in the bloodstream when physical activity is prolonged and intensive, cortisol may only exert negative effects under these circumstances.

The harmful effects of the exercise-induced inflammatory response and that of the HPA axis can be counteracted by sufficient rest and proper nutrition. Therefore, the short- and long-term detrimental consequences associated with exercise-induced inflammation and the

successive HPA axis activation may be avoided. The post-exercise recovery period is essential for reducing fatigue and adapting to physical activity (Smith, 2003a). Two levels of "rest-recovery" exist and are defined as the following: 1) "in reference to the amount of time between exercise sessions on a daily basis", and 2) "in reference to the amount of time between longer cycles or periods of training" (Smith, 2003a, p. 1108). Proper nutrition entails the quality and quantity of food consumed, daily and before, during (if necessary), and following physical activity (Smith, 2003a). Proper nutrition also includes ingesting daily requirements of macronutrients (protein, carbohydrates, and fats), and micronutrients (vitamins and minerals; Smith, 2003a).

A single bout of prolonged, moderate- to high-intensity exercise only induces immune dysfunction temporarily post-exercise, more so for high-intensity training; approximately 3-72 hours (Nieman, 2003), as per the literature, which was previously discussed. Also, the 3-72 hour period simply increases the risk for URTIs, which means an individual engaging in a single bout of exercise for a prolonged period, at moderate- to high-intensity may not even encounter URTIs, or any other harmful effects of exercise-induced inflammation and the subsequent activation of the HPA axis. Thus, this immune dysfunction constitutes a short-term phenomenon that can be resolved within 3-72 hours through sufficient rest and proper nutrition. Furthermore, through sufficient rest and proper nutrition, homeostasis of all systems (immune, endocrine, reproductive systems, etc.) may be restored without experiencing harmful consequences, or without experiencing long-term detrimental effects, such as the long-term suppression of the HPG axis.

Based on the literature, the most severe detrimental effects of exercise-induced inflammation caused by over-activation of the HPA axis, such as the suppression of the HPG axis, impairment of tissue regeneration and adaptation to physical activity; occur when

individual exercise bouts are prolonged and performed at high-intensities, and executed daily for one week or more. Although the data discussed above showed an enhanced immune function for prolonged-duration, moderate-intensity training, exercise performed at this level could also be detrimental if exerted daily for one week or more. Additionally, the more severe harmful consequences are experienced when sufficient rest is not given and nutritional status is poor. In the case of endurance athletes, it is difficult to advise them to minimize their training regime. Thus, given the research, recommendations for endurance athletes are as follows: a) organize training regime that allows maximal rest, b) proper nutrition, c) hydration, d) adequate sleep, e) minimize other life stressors (psychological/mental, emotional, environmental stress), f) minimize substance use (drugs and alcohol), and g) minimize social stress; all in an attempt to mitigate further immune-suppressant effects via HPA axis stimulation. Therefore, exercise-induced inflammation instigated by prolonged-duration, moderate-intensity and prolonged-duration, high-intensity training can serve a useful purpose for endurance exercise provided that inflammation is carefully managed through the recommendations discussed above.

Medium-duration, moderate-intensity exercise does not elicit a large immune response as shown in table III, especially at an intensity less than 50% VO_{2max}. In fact, medium-duration, moderate-intensity exercise enhances the activities of immune cells rather than suppressing them. This may be due to the delayed response of cortisol secretion during exercise, and/or the clearance of cortisol from the bloodstream as it is being secreted. Hence, the exercise-induced inflammatory response and the subsequent activation of the HPA axis do not represent a threat to individuals in this case. Essentially, exercise-induced inflammation does serve a useful purpose for exercise and the post-exercise recovery period in this context. One could argue that the enhanced activities of immune cells may cause damage to host tissues; however, the response of

the HPA axis may have some control over the exercise-induced inflammatory response even though cortisol is cleared from the bloodstream as it is being secreted. Some of the cortisol secreted may bind to immune cells to modulate the immune response to a certain degree without completely suppressing immune activities while a certain percentage of cortisol is being cleared from the bloodstream. Without any modulation of the immune response via the HPA axis to a certain degree, the exercise-induced inflammatory response could possibly induce host tissue damage even during medium-duration, moderate-intensity training. No matter the duration and intensity of exercise, rest should always be targeted; however, under conditions where exercise is of medium-duration and performed at less than 50% VO_{2max}, rest could be considered at the first level only. That is, "in reference to the amount of time between exercise sessions on a daily basis", rather than "in reference to the amount of time between longer cycles or periods of training" (Smith, 2003a, p. 1108). Proper nutrition is essential as well; however, a strict nutritional schedule is unnecessary when exercise is of medium-duration and performed at less than 50% VO_{2max}.

The magnitude of the immune response is greater during medium-duration, high-intensity exercise than medium-duration, moderate-intensity training. However, an immune response of this magnitude does not appear to represent a threat to individuals. Activities of immune cells are enhanced as shown in table III, and the level of modulation of the immune response via HPA axis seems appropriate. To be specific, it appears that the level of control which the HPA axis has over the exercise-induced inflammatory response is sufficient to prevent host tissue damage by immune cells. Furthermore, the magnitude of HPA axis activation seems suitable, as immunosuppressive effects are not observed during medium-duration, high-intensity exercise. NK cells are the only innate immune cell type that are affected by medium-duration, high-

intensity training as depicted by a 40% decrease in their number 2-4 hours post-excise paralleled with a decrease in NKCA. Nevertheless, despite these phenomena, NK cell count and NKCA return to pre-exercise values and activities, respectively, after 2-4 hours; hence, not detrimental. Therefore, the exercise-induced inflammatory response during medium-duration, high-intensity exercise does serve a useful purpose for physical activity. Additionally, the exercise-induced inflammatory response does serve a useful purpose for the post-exercise recovery period. However, without sufficient rest and proper nutrition, the exercise-induced inflammatory response and the subsequent activation of the HPA axis could become harmful. The two levels of rest, which were previously discussed, should be considered when engaging in medium-duration, high-intensity exercise. Proper nutrition is also important when exercise is of medium-duration and performed at high-intensity.

4.1 Should the Exercise-Induced Inflammatory Response be Blunted?

As previously discussed, cryotherapy (ice, ice baths) is commonly used following exercise to blunt or reduce inflammation caused by injuries and/or muscle soreness (Bleakley et al., 2004). It is assumed that reducing inflammation through cryotherapy helps muscle tissues recover from injuries and/or soreness following physical activity (Bleakley et al., 2004). Additionally, RICE is a regular method used to treat soft-tissue injuries and/or muscle soreness (Quintero et al., 2009). Various nutritional means have also been used to blunt the exercise-induced inflammatory response; carbohydrate ingestion during and immediately after exercise being the most common (Gleeson et al., 2004; McFarlin et al., 2004; Mitchell et al., 1998; Nehlsen-Cannarella et al., 1997; Nieman et al., 2004; Nieman et al., 1998; Scharhag et al., 2006). However, the use of these methods may be inappropriate (Mirkin, 2014).

Dr. Gabe Mirkin coined the term RICE in 1978; however, this method has been revised (Mirkin, 2014). Dr. Mirkin explains that the healing process may be delayed by ice and complete rest as opposed to assisting recovery (Mirkin, 2014). Applying ice to injured, damaged and/or sore area(s) constricts blood vessels and reduces blood flow; thus, decreases the migration of immune cells into the affected area(s) (Mirkin, 2014). Following the application of ice, dilation of blood vessels and the return of blood flow does not occur for many hours, which may induce the necrosis of the tissue(s), and permanent nerve damage may even occur (Mirkin, 2014). Furthermore, applying ice to injured, damaged, and/or sore areas hinders the secretion of molecules, such as IGF-1, via immune cells delaying the healing process (Mirkin, 2014). Dr. Mirkin also states that any factor, which reduces or blunts inflammation, also hinders the healing process (Mirkin, 2014). These factors include the following: a) cortisone-type drugs, b) almost all medications that mitigate pain, such as non-steroidal anti-inflammatory drugs (e.g., ibuprofen), c) immune suppressants used in the treatment of arthritis, cancer or psoriasis, d) cold packs or ice, and e) any other factors blocking the immune response to damage (Mirkin, 2014). Ice or other cooling methods also decrease strength, speed, endurance and coordination (Mirkin, 2014).

RICE has commonly been replaced with METH (movement, elevation, traction, and heat) (Catanzaro, 2014). Rest and compression is not recommended; rather, movement with traction should be put into practice (Catanzaro, 2014). Resting may cause skeletal muscles to atrophy and become weak, and compression may reduce blood flow to the injured, damaged, and/or sore area(s) (Catanzaro, 2014). Nonetheless, pressure will be relieved with traction, and blood flow to the affected area(s) will occur with movement (Catanzaro, 2014). Also, combining movement with traction assists with the following: a) reducing pain levels, b) improving flexibility, and c)

restoring normal joint alignment (Catanzaro, 2014). Heat and elevation both promote blood flow to the injured, damaged, or sore area(s) (Catanzaro, 2014). Again, blood flow allows immune cells to migrate to the affected area(s) along with oxygen and nutrients (Catanzaro, 2014). Furthermore, healing factors secreted by immune cells may also be released into the affected area(s) with increased blood flow (Catanzaro, 2014); however, inducing movement through muscle contraction is essential to activate the lymphatic system for the removal of waste products and reduction in swelling (Cochrane, 2004). Solely increasing the blood circulation, by applying heat for example, does not remove waste products and reduce swelling (Cochrane, 2004). The removal of debris, or waste products, and movement of fluid contents by the lymphatic system is needed to reduce swelling, and activation of the lymphatic system is dependent on muscle contraction, or gravity, not increased blood flow (Cochrane, 2004). Much pain could be elicited by inducing muscle contraction in the exact area of injury; hence, generating muscle activation in the area of the body where the injury is located is sufficient (Catanzaro, 2014).

Nevertheless, training adaptations and subsequent exercise performance may be hindered or limited by the ingestion of carbohydrates during exercise bouts as the attenuation of the exercise-induced IL-6 response will also cause the following: a) inhibition of lipolysis, b) decline in the anti-inflammatory effects of exercise, and c) decrease in the expression of various metabolic genes, located in the exercising muscles, responsible for recovery and training adaptations (Gleeson, 2007). Arguably, athletes may work harder and longer by consuming carbohydrates during physical activity (Gleeson, 2007). However, the effects of carbohydrate intake during physical activity on training adaptations and subsequent exercise performance are unknown; thus, research regarding this issue is required (Gleeson, 2007).

Given the available research, the exercise-induced inflammatory response should not be blunted by carbohydrate ingestion during physical activity. That is, inflammation should not be blunted at all during exercise through any means, not even by the consumption of carbohydrates. As stated above, carbohydrate supplementation decreases the rise in catecholamines and ACTH (Gleeson et al., 2004; McFarlin et al., 2004), which could hinder exercise performance. If ACTH is attenuated, cortisol secretion would also be attenuated since its production is stimulated by ACTH. The attenuation of both catecholamines and ACTH could impede the mobilization of fuel during physical activity; thus, reducing energy levels for the athlete and hindering exercise performance. Additionally, decreasing plasma levels of catecholamines through carbohydrate ingestion during exercise could also reduce its effects on insulin and glucagon. To be precise, the simultaneous suppression of insulin secretion and induction of glucagon release may not be effective if catecholamines are attenuated during physical activity. As a result, energy levels may not be sufficient and exercise performance could be hampered. The consumption of carbohydrates also induces the secretion of insulin, which causes the uptake of glucose by skeletal muscles and adipose tissues (Schenk, Saberi, & Olefsky, 2008). Furthermore, insulin also inhibits the breakdown of fatty acids from adipose tissues and reduces glucose secretion from the liver (Schenk et al., 2008). Thus, again, the availability of energy could be insufficient causing a decline in exercise performance. Carbohydrate ingestion during physical activity also attenuates the rise in cytokines and leukocytes (McFarlin et al., 2004; Mitchell et al., 1998; Nehlsen-Cannarella et al., 1997; Nieman et al., 2004; Nieman et al., 1998; Scharhag et al., 2006), which may decrease the beneficial effects of the exercise-induced inflammatory response that was previously discussed.

Based on the literature, I would recommend that individuals engaging in physical activity adopt a lifestyle that entails proper nutrition. Specifically, those having an active lifestyle should consume enough calories throughout the day (i.e., before exercising) to support their physical activity level and avoid exercising in a glycogen-depleted state. Additionally, sufficient calories should be consumed following physical activity to replenish glycogen levels, avoid fatigue, and provide the energy required to heal and adapt to training. Proper nutrition should also entail the consumption of adequate calories on non-workout days to provide the body with the energy required for the healing process, adapt to training, and store energy for subsequent exercise performances. Finally, proper nutrition also includes the quality of food consumed and ingesting daily requirements of macro- and micronutrients, as stated in Smith, 2003a. Thus, active individuals should be conscientious of the type of food they ingest, and ensure that sufficient macro- and micronutrients are consumed.

4.2 Does Inflammation Serve a Useful Purpose for Exercise for Aging Individuals?

The circulating levels of pro-inflammatory mediators begin to rise in healthy individuals between the ages of 50-60 years (Fagiolo et al., 1993). Evidently, those 50 years of age or greater have a higher pro-inflammatory status than younger individuals (Freund et al., 2010).Therefore, active individuals, as defined by engaging in physical activity 4-7 days a week for a minimum of 30 minutes per day (Elsawy & Higgins, 2010), aged 50 years or greater should be conscientious of the intensity and duration of their exercise bouts. Because the health status and fitness level of each individual varies, generalizing exercise intensities and durations to the aging population is difficult; an exercise intensity and duration may be suitable for one, but unfavourable for another (Mazzeo & Tanaka, 2001). Also, the health status, fitness level, and response to the same exercise intensity and duration could differ among aging individuals of the same age (Mazzeo &

Tanaka, 2001). Hence, aging adults should consult a health care professional for the prescription of exercise, as the intensity and duration would be unique to each person (Mazzeo & Tanaka, 2001). As a general guide; however, those 50 years of age or greater should avoid high-intensity aerobic/endurance exercise, even if the duration is short to medium. The functions of innate immune cells become compromised with increasing age (Fulop et al., 2012; Gomez et al., 2005), and high-intensity aerobic/endurance exercise also induces a temporary dysfunction in innate immunity (Gleeson, 2007; Plowman & Smith, 2008). Additionally, as individuals age, responses of the innate immune system to infectious agents are slowed and weakened (Gomez et al., 2005; Plackett et al., 2004). The combined actions of the aforementioned phenomena may cause deleterious effects, such as increased risk and rate of infections and injuries, decreased ability of innate immunity to combat any form of illness (infections, viruses, parasites), and decreased capacity of the innate immune system to heal wounds and injuries. High-intensity aerobic/endurance exercise would also elicit a large immune response (McFarlin et al., 2004). An immune response of high magnitude is characterized by a high percentage of innate immune cells in the plasma paralleled with a significant increase in pro-inflammatory mediators, such as TNF-α, IL-1, and IL-6 (Plowman & Smith, 2008). The high levels of circulating innate immune cells and pro-inflammatory mediators in the blood could cause tissue damage and instigate or exacerbate autoimmune/inflammatory diseases. For example, the exercise-induced increase in circulating levels of TNF-α could instigate or exacerbate insulin resistance, as TNF-α induces insulin resistance, either on a short- or long-term basis depending if high-intensity training is temporary or chronic. Thus, aging individuals would not benefit much from exercising at high intensities.

Physical activity is beneficial to the aging population when performed at low- to moderate intensities (Mazzeo & Tanaka, 2001). As previously mentioned, regular, low-to moderate-intensity exercise reduces or suppresses low-grade systemic inflammation associated with aging (Petersen & Pedersen, 2005). Additionally, exercise may improve the quality of life of the aging population by reducing the effects of sarcopenia and/or sarcopenic obesity (Taaffe, 2006). Following are mechanisms by which exercise may reduce the level of systemic inflammation associated with the aging process (Woods et al., 2012).

As previously discussed, aging is associated with sarcopenia, the decline in muscle mass and strength (Beyer et al., 2012; Licastro et al., 2005; Moulias et al., 1999), and an increase in fat mass, which may lead to sarcopenic obesity (Kohara, 2014). Sarcopenia is largely related to frailty observed during aging (Taaffe, 2006), and the increase in fat mass instigates inflammation since macrophages are interspersed among adipose tissues (Fried et al., 1998; Harkins, 2004); macrophages increase in number as the size of fat cells enlarges (Arner & Spalding, 2010). The inflammatory response generated by macrophages contained within the extracellular space of adipose tissues contributes to systemic inflammation during the aging process (Woods et al., 2012). Physical activity constitutes an anabolic stimuli; thus, exercise may preserve or increase muscle mass and strength, or slow down the loss of muscle mass and strength during aging. If muscle mass and strength is preserved or increased, or their rate of loss is reduced, age-related frailty may also subside. Exercise also decreases the size of adipocytes, not the number; therefore, the level of systemic inflammation may also be reduced as macrophage count would decline as well (Arner & Spalding, 2010).

IL-6 represents a cytokine that plays a dual role; functioning as both a pro- and anti-inflammatory mediator (Petersen & Pedersen, 2005). This cytokine exerts its anti-inflammatory

effects following physical activity by stimulating the secretion of anti-inflammatory mediators, such as IL-1Rα and IL-10 (Petersen & Pedersen, 2005). IL-1Rα inhibits the actions of IL-1, and IL-10 influences a vast array of cytokines (Petersen & Pedersen, 2006). Furthermore, IL-6 suppresses the secretion of TNF-α, which induces insulin resistance (Greiwe, Cheng, Rubin, Yarasheski, & Semenkovich, 2001). As previously mentioned, a resulting consequence of insulin resistance includes deficiencies in nutritional reserves, which weakens immune responses (Moulias et al., 1999; Roubenoff, 2003). Therefore, suppressed secretion of TNF-α via IL-6 may allow the uptake of nutrients by cells, which could strengthen immune responses in aging individuals. Recall that approximately half of the cell mass of the human body is accounted for by muscle tissues (Welle, 2003). Therefore, a large amount of nutritional reserves, such as protein and glycogen, must mainly be stored in muscle tissues. The decline in muscle mass associated with aging could reduce the amount of space available for the storage of nutrients. This could be a mechanism by which innate immune responses are weakened, as immune cells require energy to exert their functions. The incorporation of physical activity provides a mean by which muscle mass can be maintained or increased, or the loss of muscle mass can be reduced. The preservation of muscle mass through exercise could reduce deficiencies in nutritional reserves within muscle tissues; thus, providing sufficient energy for immune responses, and strengthening the immune system.

As previously mentioned, an age-related redox imbalance, the oxidative stress hypothesis, is the most credible proposed mechanism for inflammaging (Chung et al., 2009). Regular, low- to moderate-intensity exercise may reduce the level of systemic inflammation through the reduction of oxidative stress (Chung et al., 2009). Oxidative stress is reduced by physical activity through the up-regulation of endogenous anti-oxidant defence mechanisms

(Chung et al., 2009). On the other hand, high-intensity exercise may cause the production of reactive species to exceed their scavenging by anti-oxidant defences (Slattery, Bentley, & Coutts, 2014). Therefore, this phenomenon would deregulate the immune system and exacerbate inflammatory responses causing further tissue damage (Slattery et al., 2014).

The exercise-induced inflammatory response stimulates the HPA axis inducing the secretion of cortisol (Tsigos & Chrousos, 2002). Cortisol induces anti-inflammatory effects, which can be beneficial given that exercise is regular and of moderate-intensity (Duclos & Tabarin, 2011). As discussed before, the HPA axis stimulates the secretion of cortisol under circumstances where physical activity is performed at intensities greater than 50% VO_{2max} (Chandler & Brown, 2012); between approximately 55-60% VO_{2max} (Gleeson, 2007). Thus, to receive the beneficial anti-inflammatory effects of cortisol, individuals would have to exercise at intensities greater than 50% VO_{2max}. Nevertheless, aging individuals should consult a health care professional to determine their health status and fitness level to ensure that the correct exercise intensity and duration is prescribed (Mazzeo & Tanaka, 2001). If physical activity cannot be exerted at intensities greater than 50% VO_{2max}, aging individuals may obtain the health benefits of exercise through other mechanisms mentioned above. Finally, reducing the level of systemic inflammation associated with aging through physical activity decreases the risk of developing age-related diseases, such as cardiovascular diseases, diabetes, hypertension, infections, and cancer (Barlow et al., 2006; Blair et al., 1996; Evenson, Stevens, Cai, Thomas, & Thomas, 2003; Kodama et al., 2009; Lynch et al., 1996).

The duration of physical activity pertaining to the aging population should be prolonged since the recommended intensity is low to moderate (Pate et al., 1995; Paterson & Warburton, 2010). For aging individuals, exercise performed for at least 1 hour is considered prolonged (Pate

et al., 1995; Paterson & Warburton, 2010). However, the duration of physical activity should be adjusted according to the intensity (Mazzeo & Tanaka, 2001).

Physical activity exerted at higher intensities should be performed at shorter durations (Mazzeo & Tanaka, 2001). As a general rule, nonetheless, moderate-intensity exercise should be performed for a minimum of 30 minutes per day, or at least 4-7 days a week, to attain the beneficial effects of physical activity (Elsawy & Higgins, 2010; Mazzeo & Tanaka, 2001; Nelson, Rejeski, Blair, Duncan, & Judge, 2007; Pate et al., 1995). Aging individuals should gradually increase the duration of exercise as opposed to the intensity throughout the first stages of an exercise program (Mazzeo & Tanaka, 2001). If exercise is performed at higher intensities, continuous physical activity for at least 20 minutes, 3 days a week is recommended (Nelson et al., 2007). Nevertheless, low- to moderate-intensity exercise of longer durations is recommended and more effective for aging individuals than high-intensity training of shorter durations for the following reasons: a) the rate of injuries in aging individuals is considerably lower when exercise is performed at low- to moderate intensities compared with higher intensities; and b) most aging individuals favour low- to moderate intensity exercise over high-intensity training (Mazzeo & Tanaka, 2001). Hence, low- to moderate-intensity exercise programs are better adhered to than high-intensity training programs (Mazzeo & Tanaka, 2001).

Sedentary aging individuals beginning an exercise program should start at a low-intensity and increase progressively to moderate-intensity at their own pace (i.e., "according to one's own tolerance and preference"; Mazzeo & Tanaka, 2001, p. 812). In the aging population, however, the total amount of physical activity accumulated daily is more important than the duration of a single exercise bout (Nelson et al., 2007). That is, successions of short exercise bouts ("e.g., 10 minutes of exercise 3 times daily"; Mazzeo & Tanaka, 2001, p. 813) may be accumulated during

the day as long as physical activity is performed for a total minimum of 30 minutes daily (Mazzeo & Tanaka, 2001; Nelson et al., 2007). The health benefits of physical activity are indeed conferred even if 30 minutes or more of exercise is accumulated in successions throughout the day, and even if only 30 minutes of physical activity is performed daily (Mazzeo & Tanaka, 2001; Nelson et al., 2007).

In chapter 4, whether or not the exercise-induced inflammatory response serves a useful purpose was discussed. The circumstances in which exercise-induced inflammation is beneficial and detrimental to individuals was also illustrated. The final chapter of this paper outlines the implications for the appropriate management of the exercise induced-inflammatory response as well as the gaps in the literature, recommendations for future research, and strengths and weaknesses.

Chapter 5

5.1 Implications

Different means are used to blunt the exercise-induced inflammatory response, including cryotherapy (Bleakley et al., 2004) and nutritional measures (carbohydrate supplementation) (Gleeson et al., 2004; McFarlin et al., 2004; Mitchell et al., 1998; Nehlsen-Cannarella et al., 1997; Nieman et al., 2004; Nieman et al., 1998; Scharhag et al., 2006) under conditions where muscle soreness and/or injuries occur (Bleakley et al., 2004; Nehlsen-Cannarella et al., 1997). Although the exercise-induced inflammatory response may be detrimental, it is necessary for tissue healing and performance adaptation (Kurtz et al., 1999). Therefore, the appropriate management of exercise-induced inflammation for the prevention and treatment of injuries and/or muscle soreness, and performance gains is essential. Implications for best practice are as follows:

1) Injury prevention and performance gains - a) sufficient rest between exercise bouts (i.e., "in reference to the amount of time between exercise sessions on a daily basis" (Smith, 2003a, p. 1108) and between longer training cycles (i.e., "in reference to the amount of time between longer cycles or periods of training" (Smith, 2003a, p. 1108), b) proper nutrition, c) hydration, d) adequate sleep, e) minimize other life stressors (psychological/mental, emotional, environmental stress), f) minimize substance use (drugs and alcohol), and g) minimize social stress. Regarding nutrition, carbohydrate supplementation should not be administered during physical activity in attempt to blunt the exercise-induced inflammatory response. Rather, as previously mentioned, enough calories should be consumed throughout the day (i.e., before exercising) to support physical activity and avoid exercising in a glycogen-depleted state. Additionally, sufficient calories should be consumed following physical activity to replenish

glycogen levels, avoid fatigue, and provide the energy required to heal and adapt to training. Proper nutrition should also entail the consumption of adequate calories on non-workout days to provide the body with the energy required for the healing process, adapt to training, and store energy for subsequent exercise bouts. Individuals should only consume carbohydrates during physical activity under circumstances where they feel fatigued and faintish.

2) Treatment of injuries and/or muscle soreness: Injuries and/or muscle soreness should not be treated with the common method used known as RICE. Instead, METH should be implemented to treat injuries and/or muscle soreness. Cryotherapy should not be employed to reduce inflammation in attempt to treat soft-tissue injuries and/or reduce muscle soreness following physical activity; heat should be used instead.

Regarding the aging population, those 50 years of age or greater, exercise intensity and duration should be prescribed by a health care professional for the following reasons: a) age has significant impacts on both immune function and underlying inflammatory status (Franceschi et al., 2007; Gomez et al., 2008; Weiskopf et al., 2009), b) the health status, fitness level, and response to the same exercise intensity and duration could differ among aging individuals of the same age (Mazzeo & Tanaka, 2001), c) appropriate management of the exercise-induced inflammatory response and inflammaging, and d) elicit an exercise-induced inflammatory response appropriate for the individual for healthy outcomes. As a general guide; however, those 50 years of age or greater should avoid high-intensity aerobic/endurance exercise, even if the duration is short to medium. Physical activity is beneficial to the aging population when it is prolonged (at least1 hour; Pate et al., 1995; Paterson & Warburton, 2010) and performed at low- to moderate intensities (Mazzeo & Tanaka, 2001). Nonetheless, if physical activity is performed at a high intensity, the duration should be shorter (Mazzeo & Tanaka, 2001).

5.2 Gaps in the Literature and Recommendations for Future Research

As previously discussed, the systemic inflammatory response during and immediately after exercise, and during post-exercise recovery has been studied more extensively than the local inflammatory response in muscle tissues (Peake et al., 2005). Although invasive to study, it would be valuable to know the local inflammatory response of varying exercise intensities and durations during and immediately after exercise, and during post-exercise recovery in muscle tissues for the following reasons: a) the appropriate management of local inflammatory responses for the prevention and treatment of injuries and/or muscle soreness, and optimum training adaptation, and b) understanding when the local inflammatory response is beneficial and detrimental to prevent injuries and/or muscle soreness, and decrements in training adaptation. Additionally, it would be beneficial to know how leukocytes change, before exercise to 14 days post-exercise. This descriptive data would clarify the larger picture of exercise-induced inflammation as well as the post-exercise recovery period, for both systemic and local inflammatory responses. This would provide knowledge regarding the magnitude of inflammatory responses over the long-term, and understanding of how inflammation affects physically active individuals on a long-term basis.

However, conducting such studies could be challenging for the following reasons: 1) Leukocytosis subsides 2-6 hours following physical activity; hence, relying on leukocyte count to measure inflammation could be a limitation; measuring other inflammatory mediators (e.g., cytokines) may be favourable, 2) An exercise-induced inflammatory response may not be evident up to 14 days post-exercise in individuals who have sufficient rest between exercise bouts and training cycles; thus measuring inflammation 14 days post-exercise may be difficult in such case. However, an exercise-induced inflammatory response may be evident up to 14 days

post-exercise in those who have insufficient rest between exercise bouts and training cycles; therefore, measuring inflammation 14 days post-exercise may be feasible in this case. Also, measuring inflammation up to 14 days post-exercise in individuals who have insufficient rest between exercise bouts and training cycles would be ideal to better understand the long-term effects of the exercise-induced inflammatory response. However, such studies would have to be conducted in athletes who already over-train because making subjects exercise on a daily basis without sufficient rest between exercise bouts to induce an inflammatory response for 14 days would be unethical, and 3) Keeping track of subjects for 14 days could be impractical, especially to measure local inflammation since daily muscle biopsies would have to be taken.

"A large volume of data is available relating to changes in the number of neutrophils, monocytes, and NK cells" in the blood during and immediately after exercise, and during post-exercise recovery for varying exercise intensities and durations (Peake et al., 2005, p. 67). Meanwhile, very little data is available relating to changes in other pro-inflammatory mediators, such as cytokines and acute-phase proteins, in the blood during and immediately after exercise, and during post-exercise recovery for varying exercise intensities and durations (Plowman & Smith, 2008). Solely measuring immune cell numbers in the blood does not represent the full spectrum of the exercise-induced inflammatory response. Therefore, other pro-inflammatory mediators, such as cytokines, chemokines, acute-phase proteins (serum amyloid A, fibrinogen, complement components, CRP), prostaglandins, and cell-adhesion molecules for example, should also be measured during and immediately after exercise, and during post-exercise recovery for varying exercise intensities and durations. This would provide a broader representation of the exercise-induced inflammatory response; thus, its short- and long-term effects could better be understood.

Nevertheless, apparently technical difficulties are experienced when attempting to obtain measures regarding "the response of various cytokines to exercise" (Plowman & Smith, 2008, p. 464). These technical difficulties are experienced during sample collection protocols, such as the handling, processing, and storage of samples, because these procedures are meticulous; thus, any slight deviations in the protocols can significantly affect the results (Zhou, Fragala, McElhaney, & Kuchel, 2010). Also, procedures may be specific with regards to the time of day that the sample is taken, method and duration of storage, and choice of anticoagulant (Zhou et al., 2010). However, technical difficulties, such as problems with the equipment(s), participants' behaviour(s) (e.g., refusing to give the sample), and the researcher's schedule, can interfere with obtaining measures and accurate results (Zhou et al., 2010). Additionally, the life of various cytokines is short-lived, and as a result, cytokines start to disintegrate after being extracted from the body creating challenges in attempting to obtain measurements (Zhou et al., 2010). Therefore, perhaps advanced technologies would be required to measure a broader spectrum of the exercise-induced inflammatory response.

The timeframe concerning changes in the number of circulating leukocytes in the blood for certain exercise intensities and durations is unknown as shown in table III; hence, these data should be obtained. Additionally, much of the data available regarding the changes in white blood cells, pro- and anti-inflammatory mediators during and immediately after exercise, and during post-exercise recovery for varying exercise intensities and durations are old; dating back to 2000 for example (Plowman & Smith, 2008). Therefore, recent studies should also be conducted to have up-to-date knowledge concerning exercise-induced changes in the number of leukocytes, pro- and anti-inflammatory mediators to ensure consistency in the literature.

Exercise Immunology emerged as a specific sub-discipline of the exercise sciences in the early 1990s; therefore, this area of research is fairly new (Shephard, 2010), which may very well explain the large gaps in the literature. Additionally, it was observed that around the time of major competitive events, many endurance athletes experienced minor infections, which caused anxiety about athletic performance (Shephard, 2010). Therefore, during the 1970s, sports physicians started examining whether exercise-induced alterations in immune function were responsible for these infectious diseases (Shephard, 2010). Hence, the primary purpose of the emergence of *Exercise Immunology* was to study the risks and rates of infectious diseases in athletes, mainly URTIs (Nieman, 2003; Plowman & Smith, 2008). This could provide another explanation as to why measuring the number of leukocytes in the blood is a more common methodology, than measuring other pro-inflammatory mediators during and immediately after exercise, and during post-exercise recovery for varying intensities and durations of physical activity.

As previously mentioned, carbohydrate supplementation during physical activity has been shown to attenuate the exercise-induced inflammatory response (Gleeson et al., 2004). It is speculated that training adaptations and subsequent exercise performances may be hindered or limited by the ingestion of carbohydrates during exercise bouts; however, this is unknown (Gleeson, 2007). Thus, research regarding this issue is required (Gleeson, 2007)

Finally, the use of the common method known as RICE to treat injuries, and cryotherapy to prevent or lessen muscle soreness following exercise is being reconsidered (Mirkin, 2014). This reconsideration is because these methods may delay the healing process, and hinder training adaptations and subsequent exercise performances (Mirkin, 2014). Nonetheless, research documenting these phenomena is lacking, or scarce; thus, studies should be conducted to provide

evidence for such notion. Additionally, RICE is often replaced with METH in the treatment of injuries; however, scientific studies to support this practice are lacking. The lack of evidence showing the detrimental effects of these practices may encourage individuals to continue implementing these methods to treat injuries and/or muscle soreness. Finally, the worldwide switch from RICE to METH in the treatment of injuries may be slowed or delayed without solid, scientific evidence supporting this.

Regarding the aging process, a specific pattern of increase in pro-inflammatory mediators throughout the lifespan is lacking. A congruent and stable explanation concerning the paradox of inflammaging and immunodeficiency existing concurrently during the aging process is also absent in the literature.

5.3 Strengths and Weaknesses

5.3a Strengths

The advantages and disadvantages of the exercise-induced inflammatory response are outlined, circumstances where the exercise-induced inflammatory response is beneficial and detrimental are discussed, and recommendations for appropriate management of the exercise-induced inflammatory response are provided. This information may be helpful in assisting individuals organize their training regime in a way that will prevent or reduce the risk of injuries and/or muscle soreness, and maximize training adaptations and subsequent exercise performances.

The exercise-induced inflammatory response also has beneficial and detrimental effects to aging individuals 50-60 years of age or greater that are unique to them. Therefore, understanding the age-related changes in innate immunity and how exercise affects the immune system may: 1) help aging individuals choose an exercise intensity and duration that will

minimize inflammaging and its effects, and 2) encourage the aging population to engage in daily physical activity to minimize inflammaging and its effects.

5.3b Weaknesses

The conclusions drawn by the researcher are based on available scientific literature. As noted previously, there are gaps in the literature and therefore the interpretations and recommendations may not be optimal for all segments of the population including the elderly. As a result, difficulties may arise in attempting to manage the exercise-induced inflammatory response, and organize training regime in an efficient manner to prevent or reduce the risk of injuries and/or muscle soreness, and maximize training adaptations and subsequent exercise performances.

Because the influence of aging on innate immune responses remains unclear (Aw et al., 2007; Licastro et al., 2005), difficulties may arise in attempting to manage inflammaging and its effects. Additionally, knowledge regarding a general pattern of increase in pro-inflammatory mediators across the age span is lacking in the literature. Therefore, it is difficult to devise definitive strategies that will minimize inflammaging in specific age groups.

5.4 Conclusion

The exercise-induced inflammatory response has both beneficial and detrimental effects to individuals. Therefore, the appropriate management of exercise-induced inflammation for the prevention and treatment of injuries and/or muscle soreness, and performance gains is important. Following sums up recommendations for the appropriate management of exercise-induced inflammation.

Managing the exercise-induced inflammatory response for injury prevention and performance gains should be accomplished through sufficient rest between exercise bouts and between longer training cycles, proper nutrition, hydration, adequate sleep, minimizing life

stressors, such psychological/mental, emotional, environmental and social, and minimizing substance use, such as alcohol for example.

On the other hand, managing exercise-induced inflammation to treat injuries and/or reduce muscle soreness should be attained through METH instead of RICE. Also, cryotherapy should not be used to reduce inflammation in attempt to treat soft-tissue injuries and/or reduce muscle soreness after exercise. Instead, heat should be applied to the affected area.

Carbohydrate supplementation should not be consumed during physical activity in attempt to blunt the exercise-induced inflammatory response. Instead, enough calories should be consumed throughout the day to support physical activity and avoid exercising in a glycogen-depleted state. Carbohydrates should only be consumed during exercise under conditions where individuals feel tired and faintish.

For the aging population, exercise intensities and durations should be prescribed by a health care professional, but as a general guide, those 50 years of age or greater should avoid high-intensity exercise. Physical activity is beneficial to the aging population when performed at least 4-7 days a week at low- to moderate intensities. Lastly, the duration of exercise should be adjusted according to the intensity.

Appendix A: Abbreviations

ACTH (Adrenocorticotropic hormone)

AP-1 (Activator protein-1)

ATP (Adenosine triphosphate)

AVP (Arginine-vasopressin)

CNS (Central nervous system)

CRH (Corticotropin-releasing hormone)

CRP (C-reactive protein)

DAMPs (Damage-associated molecular patterns)

DNA (Deoxyribonucleic acid)

FSH (Follicle-stimulating hormone)

GH (Growth hormone)

GnRH (Gonadotropin-releasing hormone)

HPA axis (Hypothalamic-pituitary adrenocortical axis)

HPG axis (Hypothalamic-pituitary-gonadal axis)

IGF-1 (Insulin-like growth factor 1)

IL (Interleukin)

IL-1Rα (Interleukin-1 receptor antagonist)

IL-1β (Interleukin-1 beta)

INF-γ (Interferon-gamma)

LH (Luteinizing hormone)

METH (movement, elevation, traction, and heat)

NK cells (Natural killer cells)

NKCA (Natural killer cell activity)

NF-κB (Nuclear factor kappa B)

PAMPs (Pathogen-associated molecular patterns)

PRRs (Pattern recognition receptors)

RICE (Rest, ice, compression, and elevation)

RNA (Ribonucleic acid)

RNS (Reactive nitrogen species)

ROS (Reactive oxygen species)

sIL-1Rα (Soluble IL-1 receptor antagonist)

TLRs (Toll-like receptors)

TNF-α (Tumour necrosis factor-alpha)

PVN (Paraventricular nucleus)

URTIs (Upper respiratory tract infections)

References

Abbas, A.K., Lichtman, A.H., & Pillai, S. (2007). Cellular and Molecular Immunology, 6th Edition. Philadelphia, PA: Saunders.

Agarwal, S., & Busse, P.J. (2010). Innate and adaptive immunosenescence. *Annals of Allergy, Asthma, and Immunology*, 104(3), 183-190. http://dx.doi.org/10.1016/j.anai.2009.11.009

Aggarwal, B.B., Shishodia, S., Sandur, S.K., Pandey, M.K., & Sethi, G. (2006). Inflammation and cancer: How hot is the link? *Biochemical Pharmacology*, 72(11), 1605-1621. http://dx.doi.10.1016/j.bcp.2006.06.029

Akira, S., Hirano, T., Taga, T., & Kishimoto, T. (1990). Biology of Multifunctional cytokines: IL-6 and related molecules (IL-1 and TNF). *The FASEB Journal*, 4(11), 2860-2867. http://dx.doi.10.1096/fj.1530-6860

Allen, C.L., & Bayraktutan, U. (2009). Oxidative stress and its role in the pathogenesis of ischaemic stroke. *International Journal of Stroke*, 4(6), 461-470. http://dx.doi.org/10.1111/j.1747-4949.2009.00387.x

Almeida-Oliveira, A., Smith-Carvalho, M., Porto, L.C., Cardoso-Oliveira, J., dos Santos Ribeiro, A., Falcão, R.R.,...Diamond, H.R. (2011).Age-related changes in natural killer cell receptors from childhood through old age. *Human Immunology*, 72(4), 319-329. http://dx.doi.org/10.1016/j.humimm.2011.01.009

Alvarez, E., & Santa Maria, C. (1996). Influence of the age and sex on respiratory burst of human monocytes. *Mechanisms of Ageing and Development*, 90(2), 157-161. http://dx.doi.10.1016/0047-6374(96)01763-0

Angeli, A., Minetto, M., Dovio, A., & Paccotti, P. (2004). The Overtraining Syndrome in Athletes: A Stress Related Disorder. *Journal of Endocrinological Investigation*, 27(6), 603-612. http://dx.doi.10.1007/BF03347487

Arner, P., & Spalding, K.L. (2010). Fat cell turnover in humans. *Biochemical and Biophysical Research Communications*, 396(1), 101-104. http://dx.doi:10.1016/j.bbrc.2010.02.165

Atwood, C.S., & Bowen, R.L. (2011). The reproductive-cell cycle theory of aging: An update. *Experimental Gerontology*, 46(2-3), 100-107.http://dx.doi.10.1016/j.exger.2010.09.007

Aw, D., Silva, A.B., & Palmer, D.B. (2007). Immunosenescence: emerging challenges for an ageing population. *The Journal of Cells, Molecules, Systems and Technologies*, 120(4), 435-446.http://dx.doi.org/10.1111/j.1365-2567.2007.02555.x

Baggiolini, M., & Clark-Lewis, I. (1992). Interleukin-8, a chemotactic and inflammatory cytokine. *The Journal for Rapid Publication of Short Reports in Molecular Biosciences*, 307(1), 97-101.http://dx.doi.org/10.1016/0014-5793(92)80909-Z

Balcombe, N.R., & Sinclair, A. (2001). Ageing: definitions, mechanisms and the magnitude of the problem. *Best Practice and Research Clinical Gastroenterology*, 15(6), 835-849. http://dx.doi.10.1053/bega.2001.0244

Barlow, C.E., LaMonte, M.J., FitzGerald, S.J., Kampert, J.B., Perrin, J.L., & Blair, S.N. (2005). Cardiorespiratory Fitness Is an Independent Predictor of Hypertension Incidence among Initially Normotensive Healthy Women. *American Journal of Epidemiology*, 163(2), 142-150. http://dx.doi.10.1093/aje/kwj019

Baylis, D., Bartlett, D.B., Patel, H.P., & Roberts, H.C. (2013). Understanding how we age: insights into inflammaging. *Longevity & Healthspan*, 2(1), 8. http://dx.doi.org/10.1186/2046-2395-2-8

Beckman, J.S., & Koppenol, W.H. (1996). Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and the ugly. *The American Journal of Physiology*, 271(40), C1424-C1437. Retrieved from http://ajpcell.physiology.org/content/ajpcell/271/5/C1424.full.pdf

Beckman, K.B., & Ames, B.N. (1998). The Free Radical Theory of Aging Matures. *Physiological Reviews*, 78(2), 547-581. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9562038

Beyer, I., Mets, T., & Bautmans, I. (2012).Chronic low-grade inflammation and age-related sarcopenia. *Current Opinion in Clinical Nutrition and Metabolic Care*, 15(1), 12-22.http://dx.doi.org/10.1097/MCO.0b013e32834dd297

BioHealth Diagnostics. (2004). HPA – HPT Axes. 2929 Canon St, San Diego, CA 92106. Retrieved from http://biohealthlab.com/wp-content/uploads/2011/12/HPA-HPTAxesChart.pdf

Blair, S.N., Kampert, J.B., Kohl, H.W., Barlow, C.E., Macera, C.A., Paffenbarger, R.S.,... Gibbons, L.W. (1996). Influences of Cardiorespiratory Fitness and Other Precursors on Cardiovascular Disease and All-Cause Mortality in Men and Women. *JAMA*, 276(3), 205-210. http://dx.doi:10.1001/jama.1996.03540030039029

Bleakley, C., McDonough, S., & MacAuley, D. (2004). The Use of Ice in the Treatment of Acute Soft-Tissue Injury A Systematic Review of Randomized Controlled Trials. *The American Journal of Sports Medicine*, 32(1), 251-261. http://dx.doi. 10.1177/0363546503260757

Borer, K.T. (2003). Exercise Endocrinology. United States: Library of Congress.

Borrego, F., Alonso, M.C., Galiani, M.D., Carracedo, J., Ramiredez, R., Ostos, B.,... Solana, R. (1999). NK phenotypic markers and IL2 response in NK cells from elderly people. *Experimental Gerontology*, 34(2), 253-265. http://dx.doi.org/10.1016/S0531-5565(98)00076-X

Brownlee, K.K., Moore, A.W., & Hackney, A.C. (2005). Relationship Between Circulating Cortisol and Testosterone: Influence of Physical Exercise. *Journal of Sports Science and Medicine*, 4(1), 76-83. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3880087/

Bruunsgaard, H. (2002). Effects of tumor necrosis factor-alpha and interleukin-6 in elderly populations. *European Cytokine Network*, 13(14), 389-391. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12517724

Bruunsgaard, H., Skinhoj, P., Pedersen, A.N., Schroll, M., & Pedersen, B.K. (2000). Ageing, tumour necrosis factor-alpha (TNF-α) and atherosclerosis. *The Journal of Translational Immunology*, 121(2), 255-260. http://dx.doi.10.1046/j.1365-2249.2000.01281.x

Buettner, G.R. 2011. Superoxide Dismutase in Redox Biology: The roles of superoxide and hydrogen peroxide. *Anticancer Agents Med Chem*, 11(4), 341-346. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3131414/

Burger, H.G. (2002). Androgen production in women. *Fertility and Sterility*, 77(4), 3-5.http://dx.doi.10.1016/S0015-0282(02)02985-0

Burke, K.E., & Wei, H. (2009). Synergistic damage by UVA radiation and pollutants. *Toxicology and Industrial Health*, 25(4-5), 219-224. http://dx.doi.org/10.1177/0748233709106067

Butcher, S.K., Chahal, H., Nayak, L., Sinclair, A., Henriquez, N.V., Sapey, E.,...Lord, J.M. (2001). Senescence in innate immune responses: reduced neutrophil phagocytic capacity and CD16 expression in elderly humans. *Journal of Leukocyte Biology*, 70(6), 881-886. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11739550

Cadenas, E., & Davies, K.J.A. (2000). Mitochondrial free radical generation, oxidative stress, and aging. *Free Radical Biology and Medicine*, 29(3-4), 222-230. http://dx.doi.org/10.1016/S0891-5849(00)00317-8

Candore, G., Balistreri, C.R., Grimaldi, M.P., Listì, F., Vasto, S., Caruso, M.,...Caruso, C. (2006). Opposite Role of Pro-Inflammatory Alleles in Acute Myocardial Infarction and Longevity. *ANNALS of the New York Academy of Sciences*, 1067, 270-275.http://dx.doi.org/10.1196/annals.1354.035

Candore, G., Balistreri, C.R., Bulati, M., Colonna-Romano, G., Di Bona, D., Forte, G.I.,...Caruso, C. (2009). Immune-inflammatory responses in successful and unsuccessful ageing. *G Gerontol*, 57, 145-152. Retrieved from http://www.sigg.it/public/doc/GIORNALEART/1211.pdf?r=0,6299363

Candore, G., Caruso, C., & Colonna-Romano, G. (2010). Inflammation, genetic background and longevity. *Biogerontology*, 11(5), 565-573. http://dx.doi.org/10.1007/s10522-010-9286-3

Cannizzo, E.S., Clement, C.C., Sahu, R., Follo, C., & Santambrogio, L. (2011). Oxidative stress, inflamm-aging and immunosenescence. *Journal of Proteomics*, 74(11), 2313-2323. http://dx.doi.org/10.1016/j.jprot.2011.06.005

Cannon, J.G., & St. Pierre, B.A. (1998). Cytokines in exertion-induced skeletal muscle injury. *Molecular and Cellular Biochemistry*, 179(1-2), 159-168. http://dx.doi.10.1023/A:1006828425418

Capri, M., Salvioli, S., Monti,D., Caruso, C., Candore, G., Vasto, S.,... Franceschi, C. (2008). Human longevity within an evolutionary perspective: The peculiar paradigm of a post-reproductive genetics. *Eperimental Gerontology*, 43(2), 53-60. http://dx.doi.org/10.1016/j.exger.2007.06.004

Carrasco, G.A., & Van de Kar, L.D. (2003). Neuroendocrine pharmacology of stress. *European Journal of Pharmacology*, 463(1-3), 235-272. http://dx.doi:10.1016/S0014-2999(03)01285-8

Catanzaro, J.P. (2014, December 10). The New Injury Rehabilitation Paradigm: RICE Is Not NICE, Do METH Instead! Retrieved from http://theelitetrainer.com/index.cfm?t=Blog&pi=BLOG&blid=73

Chandra, R.K. (1992). Effect of Vitamin and Trace-Element Supplementation on Immune Responses and Infection in Elderly Subjects. *The Lancet*, 340(8828), 1124-1127.http://dx.doi.org/10.1016/0140-6736(92)93151-C

Chandler, T.J., & Brown, L.E. (2008). Conditioning for Strength and Human Performance. Lippincott Williams & Wilkins. Retrieved from https://coachiwan.files.wordpress.com/2012/10/conditioning_for_strength_and_human_performance.pdf

Chrousos, G.P. (1995). The Hypothalamic–Pituitary–Adrenal Axis and Immune Mediated Inflammation. *The New England Journal of Medicine*, 332, 1351-1363.http://dx.doi.10.1056/NEJM199505183322008

Chung, H.Y., Cesari, M., Anton, S., Marzetti, E., Giovannini, S., Seo, A.Y.,... Leeuwenburgh, C. (2009). Molecular inflammation: Underpinnings of aging and age-related diseases. *Ageing Research Reviews*, 8(1), 18-30. http://dx.doi.org/10.1016/j.arr.2008.07.002

Chung, H.Y., Lee, E.K., Choi, Y.J., Kim, J.M., Kim, D.H., Zou, Y.,...Yu, B.P. (2011). Molecular Inflammation as an Underlying Mechanism of the Aging Process and Age-related Diseases. *Journal of Dental Research*, 90(7), 830-840. http://dx.doi.org/10.1177/0022034510387794

Ciz, M., Denev, P., Kratchanova, M., Vasicek, O., Ambrozova, G., & Lojek, A. (2012). Flavonoids Inhibit the Respiratory Burst of Neutrophils in Mammals. *Oxidative Medicine and Cellular Longevity*, 2012.http://dx.doi.org/10.1155/2012/181295

Cochrane, D.J. (2004). Alternating hot and cold water immersion for athlete recovery: a review. *Physical Therapy in Sport*, 5(1), 26-32.http://dx.doi:10.1016/j.ptsp.2003.10.002

Coletti, D., Moresi, V., Adamo, S., Molinaro, M., & Sassoon, D. (2005). Tumor Necrosis Factor-α Gene Transfer Induces Cachexia and Inhibits Muscle Regeneration. *The Journal of Genetics and Development*, 43(3), 120-128. http://dx.doi.10.1002/gene.20160

Consitt, L.A., Copeland, J.L., & Tremblay, M.S. (2002). Endogenous Anabolic Hormone Responses to Endurance Versus Resistance Exercise and Training in Women. *Sports Medicine*, 32(1), 1-22. http://dx.doi.10.2165/00007256-200232010-00001

Cosentino, Zaffaroni, M., Marino, F., Bombelli, R., Ferrari, M., Rasini, E.,... Frigo, G. (2002). Catecholamine production and tyrosine hydroxylase expression in peripheral blood mononuclear cells from multiple sclerosis patients: effect of cell stimulation and possible relevance for activation-induced apoptosis. *Journal of Neuroimmunology*, 133(1-2), 233-240. http://dx.doi.10.1016/S0165-5728(02)00372-7

Crétel, E., Veen, I., Pierres, A., Bongrand, P., & Gavazzi, G. (2010). Immunosenescence and infections, myth or reality? *Médecine et Maladies Infectieuses*, 40(6), 307-318. http://dx.doi.org/10.1016/j.medmal.2009.12.008

Dale, D.C., Boxer, L., & Liles, W.C. (2008). The phagocytes: neutrophils and monocytes. *Blood*, 112(4), 935-945. http://dx.doi.org/10.1182/blood-2007-12-077917

da Silva, F.O.C., & Vaz Macedo, D. (2011). Physical exercise, inflammatory process and adaptive condition: an overview. *Rev Bras Cineantropom Desempenho Hum*, 13(4), 320-328. http://dx.doi.10.5007/1980-0037.2011v13n4p320

DeLuca, C., & Olefsky, J.M. (2008). Inflammation and insulin resistance. *FEBS Letters*, 582(1), 97-105. http://dx.doi.org/10.1016/j.febslet.2007.11.057

De Martinis, M., Franceschi, C., Monti, D., & Ginaldi, L. (2005). Inflamm-ageing and lifelong antigenic load as major determinants of ageing rate and longevity. *FEBS Letter*, 579(10), 2035-2039. http://dx.doi.org/10.1016/j.febslet.2005.02.055

de Rekeneire, N., Peila, R., Ding, J., Colbert, L.H., Visser, M., Shorr, R.I.,...Harris, T.B. (2006). Diabetes, Hyperglycemia, and Inflammation in Older Individuals. *Diabetes Care*, 29(8), 1902-1908. http://dx.doi.10.2337/dc05-2327

Desler, C., Marcker, M.L., Singh, K.K. & Rasmussen, L.J. (2011). The Importance of Mitochondrial DNA in Aging and Cancer. *Journal of Aging Research*, 2011.http://dx.doi.org/10.4061/2011/407536

Dice, J.F. (1993). Cellular and Molecular Mechanisms of Aging. *Physiological Reviews*, 73(1), 149-159. Retrieved from http://physrev.physiology.org/content/physrev/73/1/149.full.pdf

Dirks, A.J., & Leeuwenburgh, C. (2006). Tumor necrosis factor α signaling in skeletal muscle: effects of age and caloric restriction. *The Journal of Nutritional Biochemistry*, 17(8), 501-508. http://dx.doi.org/10.1016/j.jnutbio.2005.11.002

Dröge, W. (2002). Free Radicals in the Physiological Control of Cell Function. *Physiological Reviews*, 82(1), 47-95. http://dx.doi.org/10.1152/physrev.00018.2001

Duclos, M., & Tabarin, A. (2011).Exercise, Training, and the Hypothalamo–Pituitary–Adrenal Axis. *Hormone Use and Abuse by AthletesEndocrine Updates*, 29, 9-15. http://dx.doi. 10.1007/978-1-4419-7014-5_2

Dunkley, P.R., Bobrovskaya, L., Graham, M.E., von Nagy-Felsobuki, E.I., & Dickson, P.W. (2004). Tyrosine hydroxylase phosphorylation: regulation and consequences. *Journal of Neurochemistry*, 91(5), 1025-1043. http://dx.doi.10.1111/j.1471-4159.2004.2797.x

Dunn, A.J. (2000). Cytokine Activation of the HPA Axis. *ANNALS of the New York Academy of Sciences*, 917, 608-617.http://dx.doi.10.1111/j.1749-6632.2000.tb05426.x

Elgert, K.D. (1996). Immunology Understanding the Immune System. New York, NY: Wiley-Liss, Inc.

Elsawy, B., & Higgins, K.E. (2010). Physical Activity Guidelines for Older Adults. *The American Academy of Family Physicians*, 81(1), 55-59. Retrieved from http://www.thehearth.net/filephotos/123/Elsawy---Higgins-2010.pdf

Enea, C., Boisseau, N., Fargeas-Gluck, M.A., Diaz, V., & Dugué, B. (2011). Circulating Androgens in Women: Exercise-Induced Changes. *Sports Medicine*, 41(1), 1-15. http://dx.doi. 10.2165/11536920-000000000-00000

Ershler, W.B., & Keller, E.T. (2000). Age-Associated Increased Interleukin-6 Gene Expression, Late-Life Diseases, and Frailty. *Annual Review of Medicine*, 51, 245-270.http://dx.doi.10.1146/annurev.med.51.1.245

Evenson, K.R., Stevens, J., Cai, J., Thomas, R., & Thomas, O. (2003). The Effect of Cardiorespiratory Fitness and Obesity on Cancer Mortality in Women and Men. *Medicine and Science in Sports and Exercise*, 35(2), 270-277.http://dx.doi:10.1249/01.MSS.0000053511.02356.72

Fagiolo, U., Cossarizza, A., Scala, E., Fanales-Belasio, E., Ortolani, C., Cozzi, E.,...Paganelli, R. (1993). Increased cytokine production in mononuclear cells of healthy elderly people. *European Journal of Immunology*, 23(9), 2375-2378.http://dx.doi.org/ 10.1002/eji.1830230950

Flaster, H., Bernhagen, J., Calandra, T., & Bucala, R. (2007). The Macrophage Migration Inhibitory Factor-Glucocorticoid Dyad: Regulation of Inflammation and Immunity. *Molecular Endocrinology*, *21*(6), 1267-1280. http://dx.doi.org/10.1210/me.2007-0065

Fox, S.I. (2009). Fundamentals of Human Physiology. New York, NY: McGraw-Hill.

Franceschi, C., Bonafè, M., & Valensin, S. (2000a). Human immunosenescence: the prevailing of innate immunity, the failing of clonotypic immunity, and the filling of immunological space. *Vaccine*, 18(16), 1717-1720. http://dx.doi.org/10.1016/S0264-410X(99)00513-7

Franceschi, C., Bonafè, M., Valensin, S., Olivieri, F., DeLuca, M., Ottaviani, E., & DeBenedictis. (2000b). Inflamm-aging: An Evolutionary Perspective on Immunosenescence. *ANNALS of the New York Academy of Sciences*, 908, 244-254. http://dx.doi.org/ 10.1111/j.1749-6632.2000.tb06651.x

Franceschi, C., Capri, M., Monti, D., Giunta, S., Olivieri, F., Sevini., F.,...Salvioli, S. (2007). Inflammaging and anti-inflammaging: A systemic perspective on aging and longevity emerged from studies in humans. *Mechanisms of Ageing and Development*, 128(1), 92-105. http://dx.doi.org/10.1016/j.mad.2006.11.016

Franceschi, C., Motta, L., Motta, M., Malaguarnera, M., Capri, M., Vasto, S.,...Caruso, C. (2008). The extreme longevity: The state of the art in Italy. *Experimental Gerontology*, 43(2), 45-52. http://dx.doi.org/10.1016/j.exger.2007.06.006

Franceschi, C., Valensin, S., Bonafè, M., Paolisso, G., Yashin, A.I., Monti, D., & De Benedictis, G. (2000c).The network and the remodeling theories of aging: historical background and new perspectives. *Experimental Gerontology*, 35(6-7), 879-896. http://dx.doi.org/10.1016/S0531-5565(00)00172-8

Freund, A., Orjalo, A.V., Desprez, P.Y., & Campisi, J. (2010). Inflammatory networks during cellular senescence: causes and consequences. *Trends in Molecular Medicine*, 16(5), 238-246. http://dx.doi.org/10.1016/j.molmed.2010.03.003

Fried, S.K., Bunkin, D.A., & Greenberg, A.S. (1998). Omental and Subcutaneous Adipose Tissues of Obese Subjects Release Interleukin-6: Depot Difference and Regulation by Glucocorticoid. *The Journal of Clinical Endocrinology and Metabolism*, 83(3), 847-850. http://dx.doi.org/10.1210/jcem.83.3.4660

Fulop, T., Fortin. C., Lesur, O., Dupuis, G., Kotb, J.R., Lord, J.M., & Larbi, A. (2012). The Innate Immune System and Aging: What is the Contribution to Immunosenescence ? *Open Longevity Science*, 6, 121-132. Retrieved from http://benthamopen.com/tolsj/articles/V006/SI0031TOLSJ/121TOLSJ.pdf

Fulop, T., Fouquet, C., Allaire, P., Perrin, N., Lacombe, G., Stankova, J.,...Dupuis, G. (1997). Changes in apoptosis of human polymorphonuclear granulocytes with aging. *Mechanisms of Ageing and Development*, 96 (1-3), 15–34. http://dx.doi.org/10.1016/S00476374(96)01881-7

Fulop, T., Larbi, A., Douziech, N., Fortin, C., Guérard, K.P., Lesur, O.,...Dupuis, G. (2004). Signal transduction and functional changes in neutrophils with aging. *Aging Cell*, 3(4), 217-226. http://dx.doi.org/10.1111/j.1474-9728.2004.00110.x

Gayoso, I., Sanchez-Correa, B., Campos, C., Alonso, C., Pera, A., Casado, J.G.,... Solana, R. (2011). Immunosenescence of Human Natural Killer Cells. *Journal of Innate Immunity*, 3(4), 337-343. http://dx.doi. 10.1159/000328005

Giunta, S. (2008). Exploring the complex relations between inflammation and aging (inflamm-aging): anti-inflamm-aging remodelling of inflamm-aging, from robustness to frailty. *Inflammation Research*, 57(12), 558-563. http://dx.doi.org/10.1007/s00011-008-7243-2.

Gleeson, M. (2007). Immune function in sport and exercise. *Journal of Applied Physiology*, 10(2), 693-699. http://dx.doi.10.1152/japplphysiol.00008.2007

Gleeson, M., & Bishop, N. (2000). Modification of immune responses to exercise by carbohydrate, glutamine and anti-oxidant supplements. *Immunology and Cell Biology*, 78, 554-561.http://dx.doi.10.1111/j.1440-1711.2000.t01-6-.x

Gleeson, M., Nieman, D.C., & Pedersen, B.K. (2004). Exercise, nutrition and immune function. *Journal of Sports Sciences*, *22*(1), 115-125. http://dx.doi.org/10.1080/0264041031000140590

Gokhale, R., Chandrashekara, S., & Vasanthakumar, K.C. (2007).Cytokine response to strenuous exercise in athletes and non-athletes—an adaptive response. *Cytokine*, 40(2), 123-127. http://dx.doi.10.1016/j.cyto.2007.08.006

Goldstein, D.S. (2010). Adrenal Responses to Stress. *Cellular and Molecular Neurobiology*, 30(8), 1433-1440. http://dx.doi.10.1007/s10571-010-9606-9

Gomez, C.R., Nomellini, V., Faunce, D.E., & Kovacs, E.J. (2008). Innate immunity and aging. *Experimental Gerontology*, 43(8), 718-728. http://dx.doi.org/10.1016/j.exger.2008.05.016

Gomez, C.R., Boehmer, E.D., & Kovacs, E.J. (2005). The aging innate immune system. *Current Opinion in Immunology*, 17(5), 457-462. http://dx.doi.org/10.1016/j.coi.2005.07.013

Gotfried, M.H. (2001). Epidemiology of clinically diagnosed community-acquired pneumonia in the primary care setting: results from the 1999–2000 respiratory surveillance program. *The American Journal of Medicine*, 111(9), 25-29. http://dx.doi.org/10.1016/S0002-9343(01)01028-2

Goto, M. (2008). Inflammaging (inflammation + aging): A driving force for human aging based on an evolutionarily antagonistic pleiotropy theory? *BioScience Trends*, 2(6), 218-230. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20103932

Greenlund, L.J.S., & Nair, K.S. (2003). Sarcopenia - consequences, mechanisms, and potential therapies. *Mechanisms of Ageing and Development*, 124(3), 287-299. http://dx.doi.org/10.1016/S0047-6374(02)00196-3

Greiwe, J.S., Cheng, B., Rubin, D.C., Yerasheski, K.E., & Semenkovich, C.F. (2001). Resistance exercise decreases skeletal muscle tumor necrosis factor α in frail elderly humans. *The FASEB Journal*, 15(2), 475-482. http://dx.doi:10.1096/fj.00-0274com

Gurgueira, S.A., Lawrence, J., Coull, B., Murthy, G.G.K., & González-Flecha, B. (2002). Rapid Increases in the Steady-State Concentration of Reactive Oxygen Species in the Lungs and Heart after Particulate Air Pollution Inhalation. *Environ Health Perspect.*, 110(8), 749-755. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1240944/

Gutteridge, J.M.C., & Halliwell, B. (2010). Antioxidants: Molecules, medicines, and myths. *Biochemical and Biophysical Research Communications*, 393(4), 561-564. http://dx.doi.org/10.1016/j.bbrc.2010.02.071

Hackney, A.C. (2006). Exercise as a stressor to the human neuroendocrine system. *Medicina (Kaunas)*, 42(10), 788-797. Retrieved from http://professor.ufop.br/sites/default/files/lenice/files/resposta_hormonal_ao_exercicio.pdf

Hackney, A.C. (2008). Effects of endurance exercise on the reproductive system of men: The "exercise-hypogonadal male condition". *Journal of Endocrinological Investigation*, 31(10), 932-938. http://dx.doi.10.1007/BF03346444

Haddad, F., Zaldivar., F., Cooper, D.M., & Adams, G.R. (2005). IL-6-induced skeletal muscle atrophy. *The Journal of Applied Physiology*, 98(3), 911-917. http://dx.doi.10.1152/japplphysiol.01026.2004

Hajishengallis, G. (2014). Aging and its impact on innate immunity and inflammation: Implications for periodontitis. *Journal of Oral Biosciences*, 56(1), 30-37. http://dx.doi.10.1016/j.job.2013.09.001

Halson, S.L., & Jeukendrup, A.E. (2004). Does Overtraining Exist? An Analysis of Overreaching and Overtraining Research. *Sports Medicine*, 34(14), 967-981. http://dx.doi.10.2165/00007256-200434140-00003

Hamid, A.A., Aiyelaagbe, O.O., Usman, L.A., Ameen, O.M., & Lawal, A. (2010). Antioxidants: Its medicinal and pharmacological applications. *African Journal of Pure and Applied Chemistry*, 4(8), 142-151. Retrieved from http://www.academicjournals.org/article/article1379499307_Hamid%20et%20al.pdf

Handschin, C., & Spiegelman, B.M. (2008). The role of exercise and PGC1α in inflammation and chronic disease. *Nature*, 454, 463-469. http://dx.doi.10.1038/nature07206

Harkins, J.M., Moustaid-Moussa, N., Chung, Y.J., Penner, K.M., Pestka, J.J., North, C.M., & Claycombe, K.J. (2004). Expression of Interleukin-6 Is Greater in Preadipocytes than in Adipocytes of 3T3-L1 Cells and C57BL/6J and *ob/ob* Mice. *The Journal of Nutrition*, 134(10), 2673-2677. Retrieved from http://jn.nutrition.org/content/134/10/2673.short

Harman, D. (2006). Free Radical Theory of Aging: An Update - Increasing the Functional Life Span. *ANNALS of the New York Academy of Sciences*, 1067, 10-21. http://dx.doi.org/10.1196/annals.1354.003

Hawke, T.J., & Garry, D.J. (2001). Myogenic satellite cells: physiology to molecular biology. *Journal of Applied Physiology*, 91(2), 534-551. Retrieved from http://jap.physiology.org/content/91/2/534

Hill, E.E., Zack, E., Battaglini, C., Viru, M., Viru, A., & Hackney, A.C. (2008). Exercise and circulating cortisol levels: The intensity threshold effect. *Journal of Endocrinological Investigation*, 31(7), 587-591. http://dx.doi.10.1007/BF03345606

Hotta, K., Niwa, M., Hara, A., Ohno, T., Wang, X., Matsuno, H.,... Uematsu, T. (2000). The loss of susceptibility to apoptosis in exudated tissue neutrophils is associated with their nuclear factor-kB activation. *European Journal of Pharmacology*, 433(1), 17-27. http://dx.doi. 10.1016/S0014-2999(01)01480-7

Huard, J., Li, Y., & Fu, F. (2002). Muscle Injuries and Repair: Current Trends in Research. *The Journal of Bone and Joint Surgery*, 85(5), 822-832. Retrieved from http://jbjs.org/content/84/5/822.extract

Izaks, G.J., & Westendorp, R.G.J. (2003). Ill or just old? Towards a conceptual framework of the relation between ageing and disease. *BMC Geriatrics*, 3(7). 1-6. http://dx.doi. 10.1186/1471-2318-3-7

Jabbour, H.N., Kelly, R.W., Fraser, H.M., & Critchley, H.O.D. (2006). Endocrine Regulation of Menstruation. *Endocrine Reviews*, 27(1), 17-46. http://dx.doi.10.1210/er.2004-0021

Jaeschke, H. (2011). Reactive oxygen and mechanisms of inflammatory liver injury: Present concepts. *Journal of Gastroenterology and Hepatology*, 26(s1), 173-179. http://dx.doi.org/10.1111/j.1440-1746.2010.06592.x

James, S.J., Rose, S., Melnyk, S., Jernigan, S., Blossom, S., Pavliv, O., & Gaylor, D.W. (2009). Cellular and mitochondrial glutathione redox imbalance in lymphoblastoid cells derived from children with autism. *The FASEB Journal*, 23(8), 2374-2383. http://dx.doi.org/10.1096/fj.08-128926

Janeway, C.A., Travers, P., Walport, M., & Shlomchik, M. (2001). Immuno biology: The Immune System in Health and Disease, 5th Edition. New York, NY: Garland Publishing.

Jensen, G.L. (2008). Inflammation: Roles in Aging and Sarcopenia. *Journal of Parenteral and Enteral Nutrition*, 32(6), 656-659. http://dx.doi.org/10.1177/0148607108324585

Kakanis, M.W., Peake, J., Brenu, E.W., Simmonds, M., Gray, B., Hooper, S.L., & Marshall-Gradisnik, S.M. (2010). The open window of susceptibility to infection after acute exercise in healthy young male elite athletes. *Exercise Immunology Review*, *16*, 119-137. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20839496

Kane, K.L., Ashton, F.A., Schmitz, J.L., & Folds, J.D. (1996). Determination of Natural Killer Cell Function by Flow Cytometry. *Clinical and Diagnostic Laboratory Immunology*, 3(3), 295-300. Retrieved from http://cvi.asm.org/content/3/3/295.full.pdf

Karalis, K., Muglia, L.J., Bae, D., Hilderbrand, H., & Majzoub, J.A. (1997). CRH and the immune system. *Journal of Neuroimmunology*, 72(2), 131-136. http://dx.doi.10.1016/S0165-5728(96)00178-6

Kirkwood, T.B.L., & Franceschi, C. (1992). Is Aging As Complex As It Would Appear? *ANNALS of the New York Academy of Sciences*, 663, 412-417.http://dx.doi.org/10.1111/j.1749-6632.1992.tb38685.x

Kodama, S., Saito, K., Tanaka, S., Maki, M., Yachi, Y., Asumi, M.,...Sone, H. (2009). Cardiorespiratory Fitness as a Quantitative Predictor of All-Cause Mortality and Cardiovascular Events in Healthy Men and Women.301(19), 2024-2035. http://dx.doi:10.1001/jama.2009.681

Kohara, K. (2014). Sarcopenic obesity in aging population: current status and future directions for research. *Endocrine*, 45(1), 15-25. http://dx.doi.org/10.1007/s12020-013-9992-0

Krishnaraj, R. (1997). Senescence and cytokines modulate the NK cell expression. *Mechanisms of Ageing and Development*, 96(1-3), 89-101. http://dx.doi.org/10.1016/S00476374(97)00045-6

Kurtz, C.A., Loebig, T.G., Anderson, D.D., DeMeo, P.J., & Campbell, P.G. (1999). Insulin-Like Growth Factor I Accelerates Functional Recovery from Achilles Tendon Injury in a Rat Model. *The American Journal of Sports Medicine*, 27(3), 363-369. Retrieved from http://ajs.sagepub.com/content/27/3/363.short

Kvetnansky, R., Pacak, K., Fukuhara, K., Viskupic, E., Hiremagalur, B., Nankova, B.,...Kopin, I.J. (1995). Sympathoadrenal System in Stress Interaction with the Hypothalamic-Pituitary-Adrenocortical System. *ANNALS of the New York Academy of Sciences*, 771, 131-158. http://dx.doi.10.1111/j.1749-6632.1995.tb44676.x

Kvorning, T., Andersen, M., Brixen, K., & Madsen, K. (2006). Suppression of endogenous testosterone production attenuates the response to strength training: a randomized, placebo-controlled, and blinded intervention study. *The American Journal of Physiology - Endocrinology and Metabolism*, 291(6), E1325-E1332, http://dx.doi.10.1152/ajpendo.00143.2006

Kyriakis, J.M., & Avruch, J. (2012). Mammalian MAPK Signal Transduction Pathways Activated by Stress and Inflammation: A 10-Year Update. *Physiological Reviews*, 92(2), 689-737. http://dx.doi.org/10.1152/physrev.00028.2011

Lanier, L.L. (2008). Up on the tightrope: natural killer cell activation and inhibition. *Nature Immunology*, 9(5), 495-502.http://dx.doi.10.1038/ni1581

Lapointe, B.M., Frenette, J., & Coté, C.H. (2002). Lengthening contraction-induced inflammation is linked to secondary damage but devoid of neutrophil invasion. *The Journal of Applied Physiology*, 92(5), 1995-2004. http://dx.doi.10.1152/japplphysiol.00803.2001

Laupland, K.B., Church, D.L., Mucenski, M., Sutherland, L.R., & Davies, H.D. (2003). Population-Based Study of the Epidemiology of and the Risk Factors for Invasive *Staphylococcus aureus* Infections. *The Journal of Infectious Disease*, 187(9), 1452-1459. http://dx.doi.org/10.1086/374621

Lavrovsky, Y., Chatterjee, B., Clark, R.A., & Roy, A.K. (2000). Role of redox-regulated transcription factors in inflammation, aging and age-related diseases. *Experimental Gerontology*, 35(5), 521-532. http://dx.doi.10.1016/S0531-5565(00)00118-2

Le Garff-Tavernier, M., Béziat, V., Decocq, J., Siguret, V., Gandjbakhch, F., Pautas, E.,...Vieillard, V. (2010). Human NK cells display major phenotypic and functional changes over the life span. *Aging Cell*, 9(4), 527-535. http://dx.doi.org/10.1111/j.14749726.2010.00584.x

Le Grand, F., & Rudnicki, M.A. (2007). Skeletal muscle satellite cells and adult myogenesis. *Current Opinion in Cell Biology*, 19(6), 628-633.http://dx.doi.10.1016/j.ceb.2007.09.012

Licastro, F., Candore, G., Lio, D., Porcellini, E., Colonna-Romano, G., Franceschi, C., & Caruso, C. (2005). Innate immunity and inflammation in ageing: a key for understanding age-related diseases. *Immunity & Ageing*, 2(8). http://dx.doi.org/10.1186/1742-4933-2-8

Ligthart, G.J., Schuit, H.R., & Hijmans, W. (1989). Natural killer cell function is not diminished in the healthy aged and is proportional to the number of NK cells in the peripheral blood. 68(3), 396-402. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1385454/

Lio, D., Scola, L., Crivello, A., Colonna-Romano, G., Candore, G., Bonafè, M.,...Caruso, C. (2003). Inflammation, genetics, and longevity: further studies on the protective effects in men of IL10 – 1082 promoter SNP and its interaction with TNF-α–308 promoter SNP. *Journal of Medical Genetics*, 40(4), 296-299. http://dx.doi.org/10.1136/jmg.40.4.296

Li, Y., & Huard, J. (2002). Differentiation of Muscle-Derived Cells into Myofibroblasts in Injured Skeletal Muscle. *The American Journal of Pathology*, 161(3), 895-907.http://dx.doi:http://dx.doi.org/10.1016/S0002-9440(10)64250-2

Lord, J.M., Butcher, S., Killampali, V., Lascelles, D., & Salmon, M. (2001). Neutrophil ageing and immunesenescence. *Mechanisms of Ageing and Development*, 122(14), 1521-1535. http://dx.doi.10.1016/S0047-6374(01)00285-8

Lundberg, U. (2005). Stress hormones in health and illness: The roles of work and gender. *Psychoneuroendocrinology*, 30(10), 1017-1021. http://dx.doi:10.1016/j.psyneuen.2005.03.014

Lynch, J., Helmrich, S.P., Lakka, T.A., Kaplan, G.A., Cohen, R.D, Salonen, R., & Salonen, J.T. (1996). Moderately Intense Physical Activities and High Levels of Cardiorespiratory Fitness Reduce the Risk of Non-Insulin-Dependent Diabetes Mellitus in Middle-aged Men. *Arch Intern Med.*, 156(12), 1307-1314. http://dx.doi:10.1001/archinte.1996.00440110073010

MacNee, W. (2011). Aging, Inflammation, and Emphysema. *The American Journal of Respiratory and Critical Care Medicine*, 184(12), 1327-1329. http://dx.doi.org/10.1164/rccm.201110-1764ED

Malm, C. (2001). Exercise-induced muscle damage and inflammation: fact or fiction? *Acta Physiologica Scandinavica*, 171(3), 233-239. http://dx.doi. 10.1046/j.1365201x.2001.00825.x

Marliss, E.B., & Vranic, M. (2002). Intense Exercise Has Unique Effects on Both Insulin Release and Its Roles in Glucoregulation: Implications for Diabetics. *The American Diabetes Association*, 51(suppl 1), S271-S283. http://dx.doi.10.2337/diabetes.51.2007.S271

Mastorakos, G., Pavlatou, M., Diamanti-Kandarakis, E., & Chrousos, G.P. (2005). Exercise and the Stress System. *Hormones*, *4*(2), 73-89. Retrieved from http://www.hormones.gr/57/article/article.html

Mazzeo, R.S., & Tanaka, H. (2001). Exercise Prescription for the Elderly Current Recommendations. *Sports Medicine*, 31(11), 809-818.http://dx.doi:10.2165/00007256-200131110-00003

McConell, G.K., Canny, B.J., Daddo, M.C., Nance, M.J., & Snow, R.J. (2000). Effect of carbohydrate ingestion on glucose kinetics and muscle metabolism during intense endurance exercise. *Journal of Applied Physiology*, 89(5), 1690-1698. Retrieved from http://jap.physiology.org/content/89/5/1690

McElhaney, J.E., & Effro, R.B. (2009). Immunosenescence: what does it mean to health outcomes in older adults? *Current Opinion in Immunology*, 21(4), 418-424. http://dx.doi.org/ 10.1016/j.coi.2009.05.023

McFarlin, B.K., Flynn, M.G., Stewart, L.K., & Timmerman, K.L. (2004). Carbohydrate intake during endurance exercise increases natural killer cell responsiveness to IL-2. *Journal of Applied Physiology*, *96*(1), 271-275. http://dx.doi.org/10.1152/japplphysiol.00585.2003

McGeer, P.L., & McGeer, E.G. (2004). Inflammation and the Degenerative Diseases of Aging. *ANNALS of the New York Academy of Sciences*, 1035, 104-116. http://dx.doi.org/10.1196/annals.1332.007

Mirkin, G. (2014, March 16). Why Ice Delays Recovery. Retrieved from http://drmirkin.com/fitness/why-ice-delays-recovery.html

Mitchell, J.B., Pizza, F.X., Paquet, A., Davis, B.J., Forrest, M.B., & Braun, W.A. (1998). Influence of carbohydrate status on immune responses before and after endurance exercise. *Journal of Applied Physiology*, *84*(6), 1917-1925. Retrieved from http://jap.physiology.org/content/84/6/1917

Mocchegiani, E., Giacconi, R., Cipriano, C., & Malavolta, M. (2009). NK and NKT Cells in Aging and Longevity: Role of Zinc and Metallothioneins. *Journal of Clinical Immunology*, 29(4), 416-425. http://dx.doi.org/10.1007/s10875-009-9298-4

Mocchegiani, E., & Malavolta, M. (2004). NK and NKT cell functions in immunosenescence. *Aging Cell*, 3(4), 177-184. http://dx.doi. 10.1111/j.1474-9728.2004.00107.x

Moulias, R., Meaume, S., & Raynaud-Simon, A. (1999). Sarcopenia, hypermetabolism, and aging. *Z Gerontol Geriat*, 32(6), 425-432. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10654381

Mourkioti, F., & Rosenthal, N. (2005). IGF-1, inflammation and stem cells: interactions during muscle regeneration. *TRENDS in Immunology*, 26(10), 535-542. http://dx.doi:10.1016/j.it.2005.08.002

Mueller, M.J., & Maluf, K.S. (2002). Tissue Adaptation to Physical Stress: A Proposed "Physical Stress Theory" to Guide Physical Therapist Practice, Education, and Research. *The Journal of the American Physical Therapy Association*, 82(4), 383-403. Retrieved from http://ptjournal.apta.org/content/82/4/383.short

National Institutes of Health - National Heart, Lung, and Blood Institute. (1998). Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report. *Obes Res*, 6(suppl 2), 51S-209S. Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK2003/pdf/TOC.pdf

Nehlsen-Cannarella, S.L., Fagoaga, O.R., Nieman, D.C., Henson, D.A., Butterworth, D.E., Schmitt, R.L.,...& Davis, J.M. (1997). Carbohydrate and the cytokine response to 2.5 h of running. *Journal of Applied Physiology*, *82*(5), 1662-1667. Retrieved from http://jap.physiology.org/content/82/5/1662

Nelson, L.R., & Bulun, S.E. (2001). Estrogen production and action. *Journal of the American Academy of Dermatology*, 45(3), S116-S124.http://dx.doi.10.1067/mjd.2001.117432

Nelson, M.E., Rejeski, W.J., Blair, S.N., Duncan, P.W., & Judge, J.O. (2007). Physical Activity and Public Health in Older Adults: Recommendation From the American College of Sports Medicine and the American Heart Association. *Circulation*, 116(9), 1094-1105. http://dx.doi.10.1161/CIRCULATIONAHA.107.185650

Newton, K., & Dixit, V.M. (2012). Signalling in Innate Immunity and Inflammation. *Cold Spring Harbor Perspectives in Biology*, *4*(3), 1-19. http://dx.doi.org/10.1101/cshperspect.a006049

Nieman, D.C. (2003). Current Perspective on Exercise Immunology. *Current Sports Medicine Reports*,*2*(5), 239-242.http://dx.doi.org/10.1007/s11932-003-0053-y

Nieman, D.C., Davis, J.M., Brown, V.A., Henson, D.A., Dumke, C.L., Utter, A.C.,...& McAnulty, L.S. (2004). Influence of carbohydrate ingestion on immune changes after 2 h of intensive resistance training. *Journal of Applied Physiology*, *96*(4), 1292-1298.http://dx.doi.org/ 10.1152/japplphysiol.01064.2003

Nieman, D.C. (1994). Exercise, upper respiratory tract infection, and the immune system. The *Official Journal of the American College Sport Medicine*, *26*(2), 128-139. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8164529

Nieman, D.C. (1997). Immune response to heavy exertion. *Journal of Applied Physiology*, *82*(5), 1385-1394. Retrieved from http://jap.physiology.org/content/82/5/1385

Nieman, D.C., Nehlsen-Cannarella, S.L., Fagoaga, O.R., Henson, D.A., Utter, A., Davis, J.M.,...& Butterworth, D.E. (1998). Effects of mode and carbohydrate on the granulocyte and monocyte response to intensive, prolonged exercise. *Journal of Applied Physiology*, *84*, 1252-1259. Retrieved from http://jap.physiology.org/content/84/4/1252.full-text.pdf+html

Nieman, D.C. (1997). Risk of Upper Respiratory Tract Infection in Athletes: An Epidemiologic and Immunologic Perspective. *Journal of Athletic Training*, *32*(4), 344-349. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16558471

Nindl, B.C., Kraemer, W.J., Deaver, D.R., Peters, J.L., Marx, J.O., Heckman, J.T., & Loomis, G.A. (2001). LH secretion and testosterone concentrations are blunted after resistance exercise in men. *Journal of Applied Physiology*, 91(3), 1251-1258. Retrieved from http://jap.physiology.org/content/91/3/1251

Ogata, K., An, E., Shioi, Y., Nakamura, K., Luo, S., Yokose, N., & Dan, K. (2001). Association between natural killer cell activity and infection in immunologically normal elderly people. *Clinical and Experimental Immunology*, 124(3), 392-397. http://dx.doi.org/10.1046/j.1365-2249.2001.01571.x

O'Mahony, L., Holland, J., Jackson, J., Feighery, C., Hennessy, T.P.J., & Mealy, K. (1998). Quantitative intracellular cytokine measurement: age-related changes in pro-inflammatory cytokine production. *Clinical and Experimental Immunology*, 113(2), 213-219. http://dx.doi.10.1046/j.1365-2249.1998.00641.x

Opal, S.M., & DePalo, V.A. (2000).Anti-Inflammatory Cytokines. *Chest Journal*, 117(4), 1162-1172.http://dx.doi.10.1378/chest.117.4.1162

Pamplona, R., & Barja, G. (2007). Highly resistant macromolecular components and low rate of generation of endogenous damage: Two key traits of longevity. *Ageing Research Reviews*, 6(3), 189-210. http://dx.doi.org/10.1016/j.arr.2007.06.002

Panda, A., Arjona, A., Sapey, E., Bai, F., Fikrig, E., Montgomery, R.R.,...Shaw, A.C. (2009). Human innate immunosenescence: causes and consequences for immunity in old age. *Trends in Immunology*, 30(7), 325-333. http://dx.doi.org/10.1016/j.it.2009.05.004

Pascual, F. B., McGinley, E. L., Zanardi, L. R., Cortese, M. M., & Murphy, T. V. (2003) Tetanus Surveillance – United States, 1998 – 2000. MMWR *Surveillance Summaries*, 52(SS03), 1-8. Retrived from http://www.cdc.gov/MMWR/PREVIEW/MMWRHTML/ss5203a1.htm

Pate, R.R., Pratt, M., Blair, S.N., Haskell, W.L., Macera, C.A., Bouchard, C.,...Wilmore, J.H. (1995). Physical Activity and Public Health A Recommendation From the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA*, 273(5), 402-407. http://dx.doi:10.1001/jama.1995.03520290054029

Paterson, D.H., & Warburton, D.E.R. (2010). Review Physical activity and functional limitations in older adults: a systematic review related to Canada's Physical Activity Guidelines. *International of Behavioural Nutrition and Physical Activity*, 7(38). http://dx.doi. 10.1186/1479-5868-7-38

Paulsen, G., Ramer Mikkelsen, U., Raastad, T., & Peake, J.M. (2012). Leucocytes, cytokines and satellite cells: what role do they play in muscle damage and regeneration following eccentric exercise? *Exercise Immunology Review*, *18*, 42-97. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22876722

Pavlov, V.A., Wang, H., Czura, C.J., Friedman, S.G., & Tracey, K.J. (2003). The Cholinergic Anti-inflammatory Pathway: A Missing Link in Neuroimmunomodulation. *Molecular Medicine*, *9*(5-8), 125-134. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1430829/

Peake, Nosaka, & Suzuki. (2005). Characterization of inflammatory responses to eccentric exercise in humans. *Exercise Immunology Review*, 11, 64-85. Retrieved from http://ro.ecu.edu.au/cgi/viewcontent.cgi?article=3979&context=ecuworks

Pedersen, B.K., & Hoffman-Goetz. (2000). Exercise and the Immune System: Regulation, Integration, and Adaptation. *Physiological Review*, 80(3), 1055-1081. Retrieved from http://physrev.physiology.org/content/80/3/1055.short

Pedersen, B.K., Steensberg, A., & Schjerling, P. (2001). Muscle-derived interleukin-6: possible biological effects. *Journal of Physiology*, 536(2), 329-337. Retrieved from http://onlinelibrary.wiley.com/doi/10.1111/j.1469-7793.2001.0329c.xd/pdf

Peel, N., Bartlett, H., & McClure, R. (2004). Healthy ageing: how is it defined and measured? *Australasian Journal on Ageing*, 23(3), 115-119. http://dx.doi.10.1111/j.1741-6612.2004.00035.x

Peppa, M., Koliaki, C., Nikolopoulos, P., & Raptis, S.A. (2010). Skeletal Muscle Insulin Resistance in Endocrine Disease. *Journal of Biomedicine and Biotechnology*, 2010. http://dx.doi.10.1155/2010/527850

Peper, J.S., van den Heuvel, M.P., Mandl, R.C.W., Hulshoff Pol, H.E., & van Honk, J. (2011). Sex steroids and connectivity in the human brain: A review of neuroimaging studies. *Psychoneurendocrinology*, 36(8), 1101-1113. http://dx.doi.10.1016/j.psyneuen.2011.05.004

Pérez, V.I., Bokov, A., Van Remmen, H., Mele, J., Ran, Q., Ikeno, Y., & Richardson, A. (2009). Is the oxidative stress theory of aging dead? *Biochimica et Biophysica Acta*, 1790(10), 1005-1014. http://dx.doi.org/10.1016/j.bbagen.2009.06.003

Petersen, A.M.W., & Pedersen, B.K. (2005). The anti-inflammatory effect of exercise. *The Journal of Applied Physiology*, 98(4), 1154-1162.http://dx.doi.10.1152/japplphysiol.00164.2004

Petersen, A.M.W., & Pedersen. (2006). The Role of IL-6 in Mediating the Anti-Inflammatory Effects of Exercise. *Journal of Physiology and Pharmacology*, 10, 43-51. Retrieved from http://www.jpp.krakow.pl/journal/archive/11_06_s10/articles/04_article.html

Peters, T., Weiss, J.M., Sindrilaru, A., Wang, H., Oreshkova, T., Wlaschek, M.,...Scharffetter-Kochanek, K. (2009). Reactive oxygen intermediate-induced pathomechanisms contribute to immunosenescence, chronic inflammation and autoimmunity. *Mechanisms of Ageing and Development*, 130(9), 564-587. http://dx.doi.org/10.1016/j.mad.2009.07.003

Plackett, T.P., Boehmer, E.D., Faunce, D.E., & Kovacs, E.J. (2004). Aging and innate immune cells. *Journal of Leukocyte Biology*, 76(2), 291-299. http://dx.doi.org/10.1189/jlb.1103592

Plowden, J., Renshaw-Hoelscher, M., Engleman, C., Katz, J., & Sambhara, S. (2004). Innate immunity in aging: impact on macrophage function. *Aging Cell*, 3(4), 161-167. http://dx.doi.org/10.1111/j.1474-9728.2004.00102.x

Plowman, S.A., & Smith, D.L. (2008). Exercise Physiology for Health, Fitness, and Performance. (Second Edition). Lippincott Williams & Wilkins.

Prado, C.M.M., Wells, J.C.K., Smith, S.R., Stephan, B.C.M., & Siervo, M. (2012). Sarcopenic obesity: A Critical appraisal of the current evidence. *Clinical Nutrition*, 31(5), 583-601. http://dx.doi.org/10.1016/j.clnu.2012.06.010

Prisk, V., & Huard, J. (2003). Muscle injuries and repair: The role of prostaglandins and inflammation. *Histol Histopathol*., 18(4), 1243-1256. Retrieved from https://digitum.um.es/xmlui/bitstream/10201/21506/1/Muscle%20injuries%20and%20repair.pdf

Pyne, D.B., & Burke, L.M. (2000). Carbohydrate Ingestion and the Immune System During Prolonged Exercise. *International Sport Med Journal*, *1*(4). Retrieved from http://reference.sabinet.co.za/sa_epublication_article/ismj_v1_n4_a4

Quintero, A.J., Wright, V.J., Fu, F.H., & Huard, J. (2009). Stem Cells for the Treatment of Skeletal Muscle Injury. *Clinics in Sports Medicine*, 28(1), 1-11. http://dx.doi.org/10.1016/j.csm.2008.08.009

Rando, T.A. (2013). The Ins and Outs of Aging and Longevity. *The Annual Review of Physiology*, 75, 617-619. http://dx.doi.org/10.1146/annurev-physiol-092712-103439

Rattan, S.I.S. (2008). Hormesis in aging. *Ageing Research Reviews*, 7(1), 63-78. http://dx.doi.org/10.1016/j.arr.2007.03.002

Renshaw, M., Rockwell, J., Engleman, C., Gewirtz, A., Katz, J., & Sambhara, S. (2002). Cutting Edge: Impaired Toll-Like Receptor Expression and Function in Aging. *The Journal of Immunology*, 169(9), 4697-4701. http://dx.doi.org/10.4049/jimmunol.169.9.4697

Ricciotti, E., & FitzGerald, G.A. (2011). Prostaglandins and Inflammation. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 31, 986-1000. http://dx.doi.10.1161/ATVBAHA.110.207449

Roubenoff, R. (2003). Sarcopenia: Effects on Body Composition and Function. *The Journals of Gerontology*, 58(11), M1012-M1017. http://dx.doi.org/10.1093/gerona/58.11.M1012

Roubenoff, R., Harris, T.B., Abad, L.B., Wilson, P.W.F., Dallal, G.E., Dinarello, C.A. (1998). Monocyte Cytokine Production in an Elderly Population: Effect of Age and Inflammation. *The Journal of Gerontology*, 53A(1), M20-M26. http://dx.doi.10.1093/gerona/53A.1.M20

Ruiz, M., Ewig, S., Marco, M.A., Martinez, J.A., Arancibia, F., Mensa, J., & Torres, A.(1999). Etiology of Community-Acquired Pneumonia: Impact of Age, Comorbidity, and Severity. *ATS Journals*, 160(2), 397-405. Retrieved from http://www.atsjournals.org/doi/abs/10.1164/ajrccm.160.2.9808045#.VK76eSvF8no

Sadeghi, H.M., Schnelle, J.F., Thomas, J.K., Nishanian, P., & Fahey, J.L. (1999). Phenotypic and functional characteristics of circulating monocytes of elderly persons. *Experimental Gerontology*, 34(8), 959-970. http://dx.doi.10.1016/S0531-5565(99)00065-0

Salminen, A., Huuskonen, J., Ojala, J., Kauppinen, A., Kaarniranta, K., & Suuronen, T. (2008). Activation of innate immunity system during aging: NF-kB signaling is the molecular culprit of inflamm-aging. *Ageing Research Reviews*, 7(2), 83-105. http://dx.doi.org/ 10.1016/j.arr.2007.09.002

Salminen, A., Kaarniranta, K., & Kauppinen, A. (2012). Inflammaging: disturbed interplay between autophagy and inflammasomes. *Aging (Albany NY)*, 4(3), 166-175. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22411934

Samols, D., Agrawal, A., & Kushner. (2002). Acute Phase Proteins. In: Oppenheim JJ, Feldman M, editors. *Cytokine Reference On-Line*. London, UK: Academic Press. http://dx.doi.10.1006/rwcy.2002.0213

Sansoni, P., Cossarizza, A., Brianti, V., Fagnoni, F., Snelli, G., Monti D.,... Franceschi, C. (1993). Lymphocyte Subsets and Natural Killer Cell Activity in Healthy Old People and Centenarians. *Blood*, 82(9), 2767-2773. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8219229

Sansoni, P., Vescovini, R., Fagnoni, F.F., Akbar, A., Arens, R., Chiu, Y.L.,...Riddell, N.E. (2014). New advances in CMV and immunosenescence. *Experimental Gerontology*, 55, 54-62. http://dx.doi.org/10.1016/j.exger.2014.03.020

Schaap, L.A., Pluijm, S.M.F., Deeg, D.J.H., & Visser, M. (2006). Inflammatory Markers and Loss of Muscle Mass (Sarcopenia) and Strength. *The American Journal of Medicine*, 119(6), 526.e9-526.e17. http://dx.doi.org/10.1016/j.amjmed.2005.10.049

Scharhag, J., Myer, T., Auracher, M., Gabriel, H.H., & Kindermann, W. (2006). Effects of Graded Carbohydrate Supplementation on the Immune Response in Cycling. *Med. Sci. Sports Exerc.*,*38*(2), 286-292. http://dx.doi.org/10.1249/01.mss.0000191437.69493.d4

Schenk, S., Saberi, M., & Olefsky, J.M. (2008). Insulin sensitivity: modulation by nutrients and inflammation. *J. Clin. Invest.*, 118(9), 2992-3002. http://dx.doi:10.1172/JCI34260

Schultz, E., & McCormick, K.M. (1994). Skeletal Muscle Satellite Cells. *Reviews of Physiology, Biochemistry and Pharmacology*, 123, 213-257.http://dx.doi.10.1007/BFb0030904

Shaw, A.C., Joshi, S., Greenwood, H., Panda, A., & Lord, J.M. (2010). Aging of the innate immune system. *Current Opinion in Immunology*, 22(4), 507-513. http://dx.doi.org/ 10.1016/j.coi.2010.05.003

Shaw, A.C., Panda, A., Joshi, S.R., Qian, F., Allore, H.G., & Montgomery, R.R. (2011). Dysregulation of human Toll-like receptor function in aging. *Ageing Research Reviews*, 10(3), 346-353. http://dx.doi.org/10.1016/j.arr.2010.10.007

Shephard, R.J. (2010). Development of the discipline of exercise immunology. *Exercise Immunology Review*, *16*, 194-222. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20839500

Siewert, E., Dietrich, C.G., Lammert, F., Heinrich, P.C., Matern, S., Gartung, C., & Geier, A. (2004). Interleukin-6 regulates hepatic transporters during acute-phase response. *Biochemical and Biophysical Research Communications*, 322(1), 232-238. http://dx.doi.10.1016/j.bbrc.2004.07.102

Sikora, E., Scapagnini, G., & Barbagallo, M. (2010). Curcumin, inflammation, ageing and age-related diseases. *Immunity and Ageing*, 7(1), 1-4. http://dx.doi.10.1186/1742-4933-7-1

Simpson, E., Rubin, G., Clyne, C., Robertson, K., O'Donnell, L., Jones, M., & Davis, S. (2000). The Role of Local Estrogen Biosynthesis in Males and Females. *Trends in Endocrinology and Metabolism*, 11(5), 184-188. http://dx.doi.org/10.1016/S1043-2760(00)00254-X

Singh, A., Failla, M.L., & Deuster, P.A. (1994). Exercise-induced changes in immune function: effects of zinc supplementation. *The Journal of Applied Physiology*, 76(6), 2298- 2303. Retrieved from http://www.researchgate.net/profile/Mark_Failla/publication/15270087Exercise-induced_changes_in_immune_function_effects_of_zinc_supplementation/links/5421602d0cf2ce3a91b714a3.pdf

Singh, T., & Newman, A.B. (2011). Inflammatory markers in population studies of aging. *Ageing Research Reviews*, 10(30), 319-329. http://dx.doi.org/10.1016/j.arr.2010.11.002

Slattery, K., Bentley, D., & Coutts, A.J. (2014). The Role of Oxidative, Inflammatory and Neuroendocrinological Systems During Exercise Stress in Athletes: Implications of Antioxidant Supplementation on Physiological Adaptation During Intensified Physical Training.45(4), 453-471.http://dx.doi.10.1007/s40279-014-0282-7

Smith, D.J. (2003a). A Framework for Understanding the Training Process Leading to Elite Performance. *Sports Medicine*, 33(15), 1103-1126.http://dx.doi:10.2165/00007256-200333150-00003

Smith, L.L. (2003b). Overtraining, Excessive Exercise, and Altered Immunity. *Sports Medicine*, 33(5), 347-364. http://dx.doi.10.2165/00007256-200333050-00002

Sohal, R.S., Mockett, R.J., & Orr, W.C. (2002). Mechanisms of aging: an appraisal of the oxidative stress hypothesis. *Free Radical Biology and Medicine*, 33(5), 575-586. http://dx.doi.org/10.1016/S0891-5849(02)00886-9

Sohal, R.S., & Orr, W.C. (2012). The redox stress hypothesis of aging. *Free Radical Biology and Medicine*, 52(3), 539-555. http://dx.doi.org/10.1016/j.freeradbiomed.2011.10.445

Srikrishna, G., & Freeze, H.H. (2009). Endogenous Damage-Associated Molecular Pattern Molecules at the Crossroads of Inflammation and Cancer. *Neoplasia*, *11*(7), 615-628. http://dx.doi.org/10.1593/neo.09284

Steensberg, A., Fischer, C.P., Keller, C., Moller, K., & Pedersen, B.K. (2003). IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. *American Journal of Physiology - Endocrinology and Metabolism*, 285(2), E433-E437. http://dx.doi.10.1152/ajpendo.00074.2003

Stratakis, C.A., & Chrousos, G.P. (1995). Neuroendocrinology and Pathophysiology of the Stress System. *Annals of the New York Academy of Sciences*, 771, 1-18. http://dx.doi.10.1111/j.1749-6632.1995.tb44666.x

Swift, M.E., Burns, A.L., Gray, K.L., & DiPietro, L.A. (2001). Age-Related Alterations in the Inflammatory Response to Dermal Injury. *The Journal of Investigative Dermatology*, 117(5), 1027-1035. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11710909

Taaffe, D.R. (2006). Sarcopenia Exercise as a treatment strategy. *The Australian Family Physician*, 35(3), 130-133. Retrieved from http://www.luzimarteixeira.com.br/wp-content/uploads/2011/04/sarcopenia-e-exercicio-2.pdf

Tidball, J.G. (2005). Inflammatory processes in muscle injury and repair. *The American Journal of Physiology*, 288(2), R345-R353.http://dx.doi.10.1152/ajpregu.00454.2004

Tidball, J.G., & Villalta, S.A. (2010). Regulatory interactions between muscle and the immune system during muscle regeneration. *The American Journal of Physiology*, 298(5),R1173-R1187.http://dx.doi.10.1152/ajpregu.00735.2009

Timmons, B.W. & Cieslak, T. (2008). Human Natural Killer Cell Subsets and Acute Exercise: A Brief Review. *Exercise Immunology Review*, 14, 8-23. Retrieved from http://www.researchgate.net/profile/Brian_Timmons/publication/23993517_Human_natural_killer_cell_subsets_and_acute_exercise_a_brief_review/links/0c9605358ff07a23b8000000.pdf

Tremblay, M.S., Warburton, D.E.R., Janssen, I., Paterson, D.H., Latimer, A.E., Rhodes, R.E.,... Duggan, M. (2011). New Canadian Physical Activity Guidelines. *Applied Physiology Nutrition and Metabolism*, 36(1), 36-46. http://dx.doi.10.1139/H11-009

Trifunovic, A., Wredenberg, A., Falkenberg, M., Spelbrink, J.N., Rovio, A.T., Bruder, C.E.,... Larsson, N.G. (2004). Premature ageing in mice expressing defective mitochondrial DNA polymerase. *Nature*, 429, 417-423. http://dx.doi.org/10.1038/nature02517

Troen, B.R. (2003). The Biology of Aging. *The Mount Sinai Journal of Medicine*, 70(1), 3-22. Retrieved from http://163.178.103.176/Fisiologia/Integra/Objetivo6/Biologia%20del%20envejecimiento.pdf

Tsigos, C., & Chrousos, G.P. (2002). Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. *Journal of Psychosomatic Research*, *53*(4), 865-871.http://dx.doi.org/10.1016/S0022-3999(02)00429-4

Valacchi, G., Sticozzi, C., Pecorelli, A., Cervellati, F., Cervellati, C., & Maioli, E. (2012). Cutaneous responses to environmental stressors. *ANNALS of the New York Academy of Sciences*, 1271, 75-81.http://dx.doi.org/10.1111/j.1749-6632.2012.06724.x

Valko, M., Leibfritz, D., Moncol, J., Cronin, M.T.D., Mazur, M., & Telser, J. (2007). Free radicals and antioxidants in normal physiological functions and human disease. *The International Journal of Biochemistry & Cell Biology*, 39(1), 44-84. http://dx.doi.org/10.1016/j.biocel.2006.07.001

Valko, M., Rhodes, C.J., Moncol, J., Izakovic, M., & Mazur, M. (2006). Free radicals, metals and antioxidants in oxidative stress-induced cancer. *Chemico-Biological Interactions*, 160(1), 1-40. http://dx.doi.org/10.1016/j.cbi.2005.12.009

Vallejo, A.N., Mueller, R.G., Hamel, D.L., Way, A., Dvergsten, J.A., Griffin, P., & Newman, A.B. (2011). Expansions of NK-like αβT cells with chronologic aging: Novel lymphocyte effectors that compensate for functional deficits of conventional NK cells and T cells. *Ageing Research Reviews*, 10(3), 354-361. http://dx.doi.org/10.1016/j.arr.2010.09.006

Vasto, S., Carruba, G., Lio, D., Colonna-Romano, G., DiBona, D., Candore, G., & Caruso, C. (2009). Inflammation, ageing and cancer. *Mechanisms of Ageing and Development*, 130(1-2), 40-45.http://dx.doi.org/10.1016/j.mad.2008.06.003

Vingren, J.L., Kraemer, W.J., Ratamess, N.A., Anderson, J.M., Volek, J.S., & Maresh, C.M. (2010). Testosterone Physiology in Resistance Exercise and Training. *Sports Medicine*, 40(12), 1037-1053.http://dx.doi.10.2165/11536910-000000000-00000

Vivier, E., Tomasello, E., Baratin, M., Walzer, T., & Ugolini, S. (2008). Functions of natural killer cells. *Nature Immunology*, 9(5), 503-510. http://dx.doi. 10.1038/ni1582

Volanakis, J.E. (2001). Human C-reactive protein: expression, structure, and function. *Molecular Immunology*, 38(2-3), 189-197. http://dx.doi.10.1016/S0161-5890(01)00042-6

Volek, J.S. (2004). Influence of Nutrition on Responses to Resistance Training. *Med. Sci. Sports Exerc.*,*36*(4), 689-696. http://dx.doi.org/10.1249/01.MSS.0000121944.19275.C4

Walrand, S., Guillet, C., Salles, J., Cano, N., & Boirie, Y. (2011). Physiopathological Mechanism of Sarcopenia. *Clinics in Geriatrics Medicine*, 27(3), 365-385. http://dx.doi.org/10.1016/j.cger.2011.03.005

Warren, M.P., & Perlroth, N.E. (2001). The effects of intense exercise on the female reproductive system. *Journal of Endocrinology*, 170, 3-11.http://dx.doi:10.1677/joe.0.1700003

Watson, M.L., White, A.M., Campbell, E.M., Smith, A.W., Uddin, J., Yoshimura, T., & Westwick, J. (1999). Anti-Inflammatory Actions of Interleukin-13.20(5), 1007-1012. http://dx.doi.10.1165/ajrcmb.20.5.3540

Wang, H.J., Zakhari, S., & Jung, M.K. (2010). Alcohol, inflammation, and gut-liver-brain interactions in tissue damage and disease development. *The World Journal of Gastroenterology*, 16(11), 1304-1313.http://dx.doi.org/10.3748/wjg.v16.i11.1304

Waugh, D.J.J., & Wilson, C. (2008). The Interleukin-8 Pathway in Cancer. *Clinical Cancer Research*, 14(21), 6735-6741. http://dx.doi.10.1158/1078-0432.CCR-07-4843

Weinert, B.T., & Timiras, P.S. (2003). Invited Review: Theories of aging. *Journal of Applied Physiology*, 95(4), 1706-1716.http://dx.doi.10.1152/japplphysiol.00288.2003

Weiskopf, D.,Weinberger, B., & Grubeck-Loebenstein, B. (2009). The aging of the immune system. *Transplant International*, 22(11), 1041-1050. http://dx.doi.org/10.1111/j.1432-2277.2009.00927.x

Weng, N.P. (2006). Aging of the Immune System: How Much Can the Adaptive Immune System Adapt? *Immunity*, 24(5), 495-499. http://dx.doi.10.1016/j.immuni.2006.05.001

Welle, S., Brooks, A.I., Delehanty, J.M., Needler, N., & Thornton, C.A. (2003). Gene expression profile of aging in human muscle. *Physiological Genomics*, 14(2), 149-159. http://dx.doi.org/10.1152/physiolgenomics.00049.2003

Wessels, I., Jansen. J., Rink, L., & Uciechowski, P. (2010). Immunosenescence of Polymorphonuclear Neutrophils. *The Scientific World Journal*, 10, 145-160.http://dx.doi.org/10.1100/tsw.2010.14

Witko-Sarsat, V., Rieu, P., Descamps-Latscha, B., Lesavre, P., & Halbwachs-Mecarelli, L. (2000). Neutrophils: Molecules, Functions and Pathophysiological Aspects. *Laboratory Investigation*, 80(5), 617-653. Retrieved from http://www.nature.com/labinvest/journal/v80/n5/abs/3780067a.html

Woods, J.A., Wilund, K.R., Martin, S.A., & Kistler, B.R. (2012). Exercise, Inflammation and Aging. *Aging and Disease*, 3(1), 130-140. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3320801/

Yin, H., Price, F., & Rudnicki, M.A. (2013). Satellite Cells and the Muscle Stem Cell Niche. *Physiological Reviews*, 93(1), 23-67. http://dx.doi.10.1152/physrev.00043.2011

Yoshikawa, T.T. (2000). Epidemiology and Unique Aspects of Aging and Infectious Diseases. *Clinical Infectious Diseases*, 30(6), 931-933. http://dx.doi.10.1086/313792

Young, H.A., & Hardy, K.J. (1995). Role of interferon-gamma in immune cell regulation. *Journal of Leukocyte Biology*, 58(4), 373-381. Retrieved from http://www.jleukbio.org/content/58/4/373.short

Yu, B.P., & Chung, H.Y. (2006). The inflammatory process in aging. *Reviews in Clinical Gerontology*, 16(3), 179-187. http://dx.doi.org/10.1017/S0959259807002110

Yu, B.P., & Yang, R. (1996). Critical Evaluation of the Free Radical Theory of Aging: A Proposal for the Oxidative Stress Hypothesis. *ANNALS of the New York Academy of Sciences*, 786, 1-11.http://dx.doi.org/10.1111/j.1749-6632.1996.tb39047.x

Zamboni, M., Mazzali, G., Fantin, F., Rossi, A., & Di Francesco, V. (2008). Sarcopenic obesity: A new category of obesity in the elderly. *Nutrition, Metabolism and Cardiovascular Diseases*, 18(5), 388-395. http://dx.doi.org/10.1016/j.numecd.2007.10.002

Zhang, Y., Wallace, D.L., de Lara, C.M., Ghattas, H., Asquith, B., Worth, A.,...Macallan, D.C. (2007). In vivo kinetics of human natural killer cells: the effects of ageing and acute and chronic viral infection. *Immunology*, 121(2), 258-265. http://dx.doi.10.1111/j.1365-2567.2007.02573.x

Zhou, X., Fragala, M.S., McElhaney, J.E., & Kuchel, G.A. (2010). Conceptual and methodological issues relevant to cytokine and inflammatory marker measurements in clinical research. *Current Opinion in Clinical Nutrition and Metabolic Care*, 13(5), 541-547. http://dx.doi.10.1097/MCO.0b013e32833cf3bc

Ziegler, M.G., Bao, X., Kennedy, B.P., Joyner, A., & Enns, R. (2002). Location, Development, Control, and Function of Extraadrenal Phenylethanolamine *N*-Methyltransferase. *ANNALS of the New York Academy of Sciences*, 971, 76-82.http://dx.doi.10.1111/j.1749-6632.2002.tb04437.x