

Immune Responses to Resistance Exercise

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ABSTRACT

Resistance exercise induces changes in leukocyte redistribution, phenotypical surface expression and leukocyte functionality. Several factors have been shown to alter the temporal pattern and/or magnitude of response including manipulation of acute program variables, the aging process, and nutritional supplementation. Rest period length and load can modify the temporal pattern and/or magnitude of leukocytosis post exercise. Aging diminishes both the duration and magnitude of the post exercise leukocytosis and reduces leukocyte functionality. The few studies that assessed the effects of nutritional supplements (e.g., carbohydrate, whey protein, caffeine) peri-resistance exercise showed minimal effects on leukocyte responses. Sex differences exist in the timing and magnitude of leukocyte infiltration into skeletal muscle. The immune response to resistance exercise is only a small part of the recovery paradigm. A better understanding of how acute program variables and other factors such as aging, sex and nutritional supplementation affect the immune response to resistance exercise is important in the context of improving recovery, performance and health.

Key Words: resistance exercise; training; immune response; leukocyte; white blood cells; neutrophil; monocyte; natural killer cell; granulocyte; lymphocyte; sex differences; gender; supplementation; immunosenescence; aging; intensity; catecholamines; cortisol; lactate; metabolic stress

Glossary of Terms:

NK cells – Natural Killer Cells;
NKCA – Natural Killer Cell Cytotoxic Activity;
RE – Resistance Exercise;
IP – Immediate Post;
PE – Post Exercise;
TNF- α – Tumor Necrosis Factor α ;
MIP-1 α – Macrophage Inflammatory Protein 1 α ;
MIP-1 β – Macrophage Inflammatory Protein 1 β ;
IFN- γ – Interferon γ ;
GM-CSF – Granulocyte Macrophage
Colony-Stimulating Factor;
G-CSF – Granulocyte Colony-Stimulating Factor;
M-CSF – Macrophage/Monocyte
Colony-Stimulating Factor;

IL-1RA – Interleukin-1 Receptor Agonist;
IL-1 β – Interleukin 1 β ;
IL-6 – Interleukin 6;
IL-10 – Interleukin 10;
VCAM-1 – Vascular Cell Adhesion Molecule 1;
ICAM-1 – Intercellular Adhesion Molecule 1;
VLA-4 – Very Late Antigen 4;
Ig – Immunoglobulin;
TLR – Toll-like Receptor;
 β_2 ADR – β_2 adrenergic receptor;
GCR – Glucocorticoid Receptor;
 ^{99m}Tc – Technetium-99m;
MPO – Myeloperoxidase;
LPS – Lipopolysaccharide;
ACTH – Adrenocorticotrophic Hormone

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INTRODUCTION

Leukocytes mediate regeneration and repair of muscle tissue after resistance exercise induced damage. Following a bout of resistance exercise natural killer cells, monocytes and neutrophils increase in the circulation. Monocytes infiltrate the tissue and differentiate into macrophages (3). Macrophages are essential for muscle repair and perform several functions such as aiding satellite cells in recruiting monocytes, stimulating satellite cell proliferation and differentiation with monocytes, promoting myogenic precursor cell survival through cell to cell adhesion and mediating extracellular matrix repair (21, 95, 136, 143). Muscle cells release chemokines which attract neutrophils to damaged tissue (143). Neutrophils aid macrophages in muscle repair by inducing oxidative damage to muscle cell membranes and by removing cellular debris along with macrophages through phagocytosis (143). NK cells may function to maintain continued recruitment of monocytes and neutrophils into the circulation through cytokine cross-talk.

The majority of resistance exercise and immune literature has focused on post exercise changes in circulating leukocyte counts. The temporal pattern and magnitude of response in circulating leukocytes is altered by manipulation of the acute program variables, age and nutritional status (11, 20, 87). Shear stress and hormonal signals (e.g., catecholamines) induce the release of leukocytes from the marginated pool but the leukocyte response is not random. Specific cells must be redistributed for specific functional purposes. By analyzing the phenotypical and functional characteristics of the cells which increase in circulation, a better understanding of why certain cell populations are increased post exercise can be deduced.

The effects of endurance exercise on the immune system has been the focus of many review articles, yet in comparison the effects of resistance training on the immune system has received little attention (15, 47, 49, 50, 82, 100, 122, 133, 152, 153). The purpose of this review is to provide a comprehensive review that focuses on the immune response to resistance exercise in humans. The immune response to resistance training is operationally defined as changes in the magnitude and temporal pattern of circulating leukocytes, changes in circulating leukocyte phenotype (e.g., surface molecules such as Ig, TLRs, adhesion molecules, etc.) and functional parameters (NKCA and proliferation). We hope this discussion provides a foundation and inspires researchers to pursue additional work in this important area to better understand the relationships between skeletal muscle and leukocytes and how resistance training can benefit both young and elderly populations.

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Leukocyte Patterns in Young Resistance Training Subjects

Introduction. A large number of studies inclusive of diverse training programs have examined the magnitude and temporal patterns of change in circulating leukocytes in response to resistance training (Table 1). Most of these studies measured leukocyte redistribution after a single bout of resistance exercise or used an acute testing exercise bout before, during and after a period of chronic training (6 months or more).

Monocytes. The most common pattern of response observed in monocytes is an increase during exercise, an early peak immediately post with a sustained monocytosis up to 120 min PE (87, 103, 116). Monocyte peak times occurred at the IP (87, 103, 134, 140) or 120 min PE time points (116). Most studies show a sustained monocytosis through the final measured time point (90-120 min), although a quicker return to baseline has been reported by 30 or 45 min PE (134, 140).

CD4 T Helper Cells. The response pattern for CD4 T helper cells to resistance exercise is variable. CD4 T cells have been shown to moderately but not significantly increase during exercise (116), result in no change (140), or result in a sustained lymphocytosis between the IP and 15 min PE time points before returning to baseline by 30 min PE (134). It is difficult to explain why CD4 T cells did not show a consistent pattern since details of the training programs used in each study were not always provided, but total volume of work may impact the CD4 T cell response (See Table 1).

CD8 Cytotoxic T Cells. The predominant CD8 T cell response is a lymphocytosis immediately post, followed by a return to baseline between 15-45 min PE

(134, 140). A different pattern of response was observed by Ramel et al 2003 where CD8 T cells decreased by approximately 14% during recovery before returning to pre-exercise levels by 120 min PE (116).

B Cells. The B cell response to resistance exercise depends on the subset being analyzed. Cells stained for CD19 represent both young immature and older mature B cells while CD20 staining represents mature B cells (78). The general acute response pattern for CD19 B cells is an increase in B cells immediately post followed by a return to baseline by 120 min PE (31, 93, 103). Since only one study measured beyond the IP time point, a narrower time frame for the return of CD19 B cells to baseline cannot be established. CD20 B cells show no significant changes in cell counts during the PE recovery period (140). It is possible that acute resistance exercise results in an increase in younger B cells in circulation.

Natural Killer Cells. NK cells respond to an acute bout of resistance exercise with a lymphocytosis during exercise (116) and immediately post (31, 93, 103, 134, 140) which is sustained until 15 min PE (134) and then either returns to baseline by 30 or 45 min PE (134, 140) or declines below baseline during the recovery period until the final time point at 120 min PE (116).

Neutrophils. The general acute response pattern of neutrophils is an increase above baseline immediately post with a sustained neutrophilia up to 120 min PE (87, 103, 116, 117, 134). Neutrophil peak times occurred immediately post (134) or at the last measured time point, either 90 (87) or 120 min PE (103, 116).

Basophils. Relatively few studies have measured and reported values for basophils after acute resistance exercise (67, 103, 134). The predominant response appears to be no change in basophils during the PE period (67, 134). Basophils have been reported to mimic the response of neutrophils, the predominant granulocyte, increasing above baseline immediately post and at the final 120 minute PE time point (103). The basophil response is associated with higher PE lactate (103).

Eosinophils. Three studies reported no changes in eosinophils within the first 30 minutes after exercise (67, 103, 134). However, one study measured eosinophils at 120 min PE and noted a decrease below baseline (103). Eosinophils show the weakest response to acute resistance exercise.

Effects of Chronic Resistance Training. Chronic resistance training is defined as performance of regular bouts of resistance exercise over a period of 6 or more months with a frequency of at least 2-3 times per week. It has been demonstrated that the type of routine (power or hypertrophy) and the workload (total body or upper body) do not affect the acute changes in the magnitude of circulating lymphocyte subsets, monocytes or neutrophils in response to a single exercise bout or augment resting levels of these leukocytes over a 6 month time period (91, 92). Since only pre to post measures were observed the possibility of differences exist-

ing between groups at later time points cannot be excluded. These studies only included women and so these results cannot be inferred to men.

Absolute Versus Relative Changes in Leukocyte Patterns. The method of reporting circulating cells can affect the results. For example Stock et al 1995 reported PE increases in total T cells, CD8 T cells, NK cells, total lymphocytes and total monocytes when expressed as absolute cell counts. However, when expressed as cell percentages, total lymphocytes, monocytes and CD8 T cells did not increase significantly PE, total T cells and CD4 T cells decreased PE and NK cells increased (140). The method of reporting changes in circulating leukocytes may especially affect lymphocytes since the dominant lymphocyte subset to change is NK cells. Immediately PE NK cells increase in magnitude by a much greater percentage than T cells or B cells, often increasing by over 200% (31, 93, 103, 140). The magnitude of the NK cell response can mask the relative response of other lymphocytes when expressed as cell percentages. Therefore absolute cell counts should be the preferred method of reporting exercise induced changes in leukocytes preferably in units of 10^9 cells/L.

Summary. Resistance exercise impacts the magnitude of circulating leukocytes. (Figure 1). Monocytes and neutrophils show an early increase at the IP time point with a sustained leukocytosis through 120 minutes PE. NK cells appear to show an early increase followed by either a quick return to baseline or a decrease below baseline.

The smaller granulocytes, basophils and eosinophils show little change, CD4 T cells do not have a general pattern and the B cell response depends on the subset. CD8 T cells show a lymphocytosis immediately PE and return to baseline as early as 15 minutes PE. Chronic resistance training appears to have no effect on circulating leukocyte counts at rest or after acute exercise regardless of training type (power vs hypertrophy) or workload (total body vs upper body) (91). Sex differences cannot be discerned chronically since these studies uti-

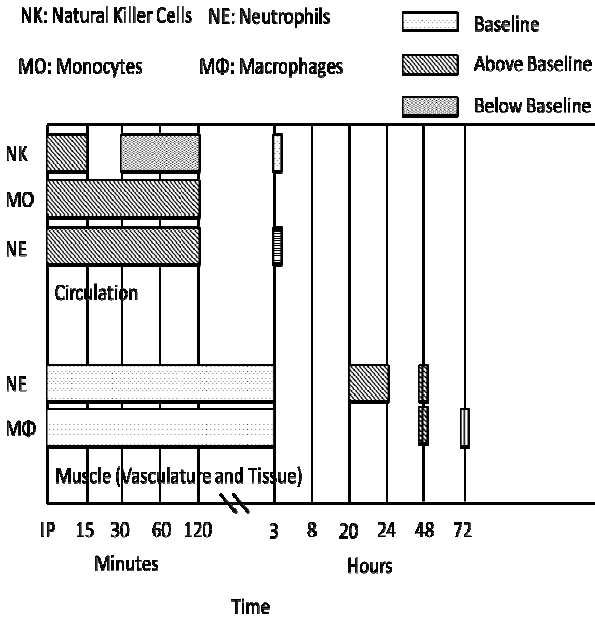


Figure 1. Temporal response patterns of selected leukocyte subsets in the circulation and muscle tissue.

lized only women. There appears to be no significant difference in the magnitude of leukocytosis after an acute bout of exercise between young trained and untrained individuals (111, 116). The method of reporting changes in circulating cell counts after RE can affect the results, especially when describing changes in lymphocytes.

The Effects of Specific Program Variables on Leukocyte Redistribution

Introduction. Skeletal muscle adaptations and the acute hormonal responses to resistance exercise are impacted by the exercise program variables (i.e., loading, rest period length, set sequence, volume, total work, exercise choice and exercise order). Manipulating these variables can impact the intensity of the training program which can be measured by physiological changes such as heart rate and lactate and scales which rate perceived exertion such as the Borg RPE scale. Manipulating these variables can also modify the magnitude and perhaps temporal pattern of circulating leukocytes PE.

Rest Period Length. Rest period length is the interval of time taken to rest between subsequent sets in a resistance training routine. The effect of rest interval length (1 vs 3 min) while maintaining the load, total work, exercise choice and exercise order has been determined (87). Resistance exercise resulted in a similar temporal pattern of increase in total leukocytes, total lymphocytes, monocytes and neutrophils regardless of time between sets, but the short rest interval resulted in a significantly greater magnitude of response PE for all leukocyte subsets (87).

Load. Load is often defined as a percentage of 1RM and has demonstrated the potential to impact the leukocyte response to resistance training. Specifically, neutrophils displayed a different response pattern to different loading conditions, indicating that neutrophils may be sensitive to changes in loading conditions. Neutrophils increased more rapidly in response to a load of 55% 1RM than 65% 1RM, however the cadence was also quicker in the higher load protocol but rest period length was the same (20).

Metabolic Response. The metabolic response to resistance exercise may impact the immune response as evidenced by a trend towards a greater increase in NK cells and significantly greater increases in CD19 B cells and CD8 and CD4 T cells in subjects who had a greater lactate response to resistance exercise (92). There were no differences in granulocytes or monocytes between high and low lactate responders (92). Lactate itself or the associated increase in acidity may impact leukocytes (59, 77, 92). Factors that determine lactate production such as inter-individual differences in muscle metabolism and manipulation of program variables may mediate the effect (35, 113, 121). Greater PE lactate levels are also associated with a greater catecholaminergic response which may also play a role in modifying cellular redistribution (113).

Future Directions. Manipulation of rest period length and load can alter leukocyte redistribution. The ideal immune response would be one that minimizes the risk of infection/onset of sickness/illness allowing for peak performance to be uninterrupted by immune compromise. This is especially crucial for athletes who compete and train during a season, a time at which maintenance of performance is crucial. The relationship between the degree of PE leukocytosis and prevention of illness/maintenance of health remains unclear. It would be valuable for future research studies to determine the impact of each program variable on leukocyte redistribution to be able to prescribe a resistance training program that will help maintain performance and health.

Effects of Dietary Factors on Resistance Exercise-Induced Leukocytosis

Nutritional supplements can modulate physical performance and may impact the immune response to resistance exercise. The majority of studies that examined the impact of dietary factors on the immune response did so in the context of acute supplementation around a single bout of resistance exercise, but a few studies utilized acute testing sessions before and after a short term training period (8-21 weeks).

Carbohydrates. The temporal pattern of monocytes and eosinophils are altered by providing carbohydrate around a bout of resistance exercise while neutrophils and basophils are unaffected. The duration of PE monocytosis was truncated to 60 minutes, half the duration observed in most studies without carbohydrate supplementation (20, 61, 87, 101, 103, 116). A quick return to baseline by 30-45 min has been observed previously after unsupplemented exercise bouts (134, 140). Eosinophils displayed an immediate PE increase with carbohydrate supplementation, which contrasts the observations made without supplementation (61, 103, 134). Total lymphocytes largely mirrored the response pattern of natural killer cells observed without supplementation indicating that NK cells dictate the response of lymphocytes. An exception was seen by Carlson et al 2008 with an increase in lymphocytes at 90 min PE (20). Although there is inconsistency among studies, the magnitude of response for neutrophils (101), monocytes (101) and total lymphocytes (20) may be attenuated by carbohydrate supplementation. The addition of a 4h time point by Koch et al 2001 also revealed a sustained neutrophilia and a return of lymphocytes to baseline at 4h PE (61). Monocytes may be sensitive to nutritional intake since all the studies which reported a shortened period of PE increase for monocytes had some form of nutritional intake prior to exercise or failed to report it (20, 61, 101, 134, 140).

Caffeine. Caffeine is a central nervous stimulant that increases circulating catecholamines, promotes lipolysis, decreases pain perception, and sustains motor unit firing rates and neuro-excitability through inhibition of adenosine (29). Since maintenance of catecholamine levels has been shown to maintain force production during resistance exercise, it is possible that the increase in catecholamines stimulated by caffeine may aid in maintaining work capacity (44). The only study that has examined the effects of caffeine on the resistance exercise-induced

immune response showed no significant difference compared to placebo in the number of circulating neutrophils, basophils, eosinophils, monocytes total leukocytes and total lymphocytes measured immediately post (80). Differences in the temporal pattern of circulating leukocyte counts could not be determined since only a single PE time point was monitored. Since caffeine increases circulating catecholamines the primary cell type affected by catecholamines would be NK cells, but NK cells were not specifically measured. Based on the findings of this study, caffeine has no effect on the IP-resistance exercise immune response.

Cystine and Theanine. Glutamine/cystine and theanine can enhance glutathione concentrations in immune cells in vitro and in the liver in vivo respectively (73, 119). NKCA is correlated with glutathione levels (62, 63). Based on these predictions it was determined that a combination cysteine and theanine supplement may have an effect on immune function after resistance training. Daily supplementation with cysteine and theanine maintained NKCA only when an unaccustomed increase in weekly training frequency occurred, but total leukocyte counts were unaffected (60).

Whey Protein. Whey supplementation has been shown to modify muscle damage, performance, perceived post-exercise fatigue and anabolic pathways in muscle fibers in conjunction with resistance training (6, 55, 57). These positive effects have mainly been attributed to the high content of essential amino acids, particularly leucine. Other whey components such as lactoferrin, glutamine, immunoglobulins, and other peptides (eg, lysozyme, β -lactoglobulin, and β -lactalbumin) have demonstrated immunoregulatory functions in animals and humans (86). Hulmi et al 2010 observed no effect of whey supplementation on neutrophils, total lymphocytes and mixed cells (monocytes, eosinophils, basophils and immature precursor cells) in young trained, young untrained and elderly trained subjects (56). Another important finding was that young untrained subjects had higher relative neutrophils, mixed cells and absolute lymphocytes than older trained subjects (56). The interpretation of this study is complicated by the fact that whey was provided to both whey and control groups PE and a standardized breakfast was not consumed consistently in all group comparisons. Whey amino acid constituents can appear in the bloodstream within 5 minutes after administration and the breakfast could have impacted the number of circulating cells, particularly monocytes (19, 20, 61, 101).

Summary. Based on the limited studies conducted it appears that supplementation with carbohydrate, protein, and caffeine has a minimal effect on the immune response to resistance exercise. Carbohydrates may attenuate the magnitude of increase in neutrophils, monocytes and total lymphocytes, but the data are inconclusive. Cystine and theanine supplementation appears to maintain NKCA only during periods of rigorous resistance training to which the athlete is unaccustomed to. Whey and caffeine were shown to have no effect on circulating leukocytes. Conclusions about the effect of nutritional supplements on the immune response to resistance exercise are limited by supplement dosage between and/or within studies, monitoring and control of diet prior to acute exercise testing and the number of PE time points. The immune response is often only characterized

by changes in circulating cell counts, but other effects such as changes in surface expression of receptors and adhesion molecules or in nucleotide and protein synthesis may also be affected.

Leukocyte Patterns in the Elderly: Effects of Immunosenescence

The aging process results in dysregulation of the immune system, known as immunosenescence, and altered hormonal responses. Immunosenescence is a two component model. The first component is a chronic increase in the levels of pro-inflammatory cytokines such as TNF- α , IL-6 and IL-1 β , pro-inflammatory markers such as C-reactive protein and clotting factors known as “inflammaging” (105). The second component is a change in cell signaling. Lipid rafts are rigid platforms in cell membranes that facilitate cell signaling by bringing signaling complexes together (132). Although the surface expression of receptors often doesn't change (129), membrane fluidity changes with aging which could lead to decreased signal complex formation and modified internal cell signaling leading to decreased leukocyte functionality. The direction of change in membrane fluidity with age is dependent on cell type. Neurons and lymphocytes in the elderly show decreases in membrane fluidity, but neutrophils in both elderly humans and rats demonstrate an increase in membrane fluidity (2, 58, 107, 147). Changes in membrane fluidity are associated with changes in membrane cholesterol, phospholipids and fatty acids. Typically membrane cholesterol is inversely related to membrane fluidity (2, 58). There are also population shifts in some leukocyte subsets. Macrophages are skewed to the alternatively activated macrophage phenotype and there is an increase in the proportion of CD56^{dim} NK cells (83). Endothelium dependent vasodilation is reduced with aging in both brachial and coronary arteries which may affect leukocyte redistribution from the marginated pool (34, 46). Aging results in changes to the circadian rhythms of several hormones such as catecholamines and cortisol (30, 146). Elderly individuals also demonstrate a modified hormonal response to resistance exercise as evidenced by diminished PE norepinephrine (11) and an increased sensitivity to ACTH, maintaining a higher level of cortisol (70). Altered leukocyte functioning, constant low grade inflammation decreased vascular plasticity, modified circadian patterns and different hormonal responses to resistance exercise all impact the differences in the immune response to resistance exercise between the young and elderly.

T Cells and B Cells. In elderly individuals, CD4 and CD8 T cells are unresponsive to resistance training. Neither resting nor the PE circulating cell numbers change after acute, short-term or chronic exercise (12, 39, 90, 115, 118). Even when controlling for total work, heavy and light loading acutely have no effect on circulating cell counts (98). Short-term training does not affect resting CD20 B cell counts, and neither short-term nor acute resistance training impacts the number of circulating CD19 B cells at rest or PE (12, 39, 115).

Natural Killer Cells. The predominant pattern of response acutely is an increase in NK cells immediately PE with a return to baseline by 2h PE (39, 90). This pattern was shown to be unaffected by short-term resistance training (39, 90). An

exception to this pattern was observed where untrained elderly subjects showed a decline in NK cell counts below baseline which returned to baseline by 6h PE (11). After short-term training the elderly subjects did not show a decrease in NK cell numbers at the IP time point and instead maintained NK cell numbers throughout the recovery period (11). Thus short-term training maintains NK cell counts after acute exercise. Several protocol differences could have contributed to the disparate results such as the prandial state of the subjects, the duration of short-term training, the acute resistance exercise tests and the sex of the subjects. Chronic resistance exercise does not affect resting NK cell levels (118). Further investigation into the morphology of circulating NK cells indicates that the predominant type of NK cells are the CD56^{dim} subset and this was not altered by chronic training (118).

Overall the NK cell response to acute exercise is reduced compared to young subjects. Although NK cells have been shown to increase after acute resistance training in the elderly, the magnitude of the PE increase is diminished compared to young individuals (11, 31, 39, 90, 103, 116, 140). Not only is the magnitude of the response different in the elderly, but so is the temporal pattern of the PE response. Regardless of training status, elderly individuals display both a diminished magnitude of response and an altered temporal pattern, but training in the elderly may partially restore the NK cell response to resistance exercise.

Neutrophils. Short-term training affects the duration of neutrophilia after acute exercise but chronic training does not impact resting neutrophil cell counts (13). Untrained elderly individuals display a transient neutrophilia at the IP time point (56). After short-term training, the neutrophilia is maintained for 30 minutes into the PE period demonstrating that short-term training increases the duration of neutrophilia after acute exercise (56). In contrast to the elderly, the acute response to resistance training in the young is a sustained neutrophilia during the exercise recovery period up to 2h PE (87, 103, 116, 134). The elderly experience an attenuated time course for neutrophilia with age, but this can be partially recovered through resistance training.

Monocytes. Monocytes respond to an acute bout of resistance exercise, but short-term training has no effect on the pattern of response and chronic training does not impact the resting monocyte cell count (13). After acute resistance exercise, a transient monocytosis occurs at the IP time point, but short-term training has no impact on this response (Although monocytes were not measured directly, they were measured in a pool of mixed cells, of which they were the predominant cell type.) (40, 56). The acute response pattern of monocytes in the elderly is reduced compared to young individuals. Acute resistance exercise elicits a sustained monocytosis in the young for 120 minutes PE (87, 103, 116, 134). The duration of monocytosis observed in the elderly is far less than that observed in the young and training does not improve this response.

Macrophages. Macrophages demonstrate both impaired functioning and decreased numbers in muscle tissue of the elderly in comparison to younger counterparts. At rest in both young and old subjects, the anti-inflammatory CD163 or

alternatively activated macrophages are more prominent than the CD11b macrophages which are the classically activated pro-inflammatory macrophages (112). Young subjects possess greater numbers of total macrophages than older subjects including greater numbers of both CD163 and CD11b macrophages. Young and elderly subjects display no change in total macrophages (CD68) 72h after a single bout of resistance exercise but young subjects demonstrate increases in both CD163 and CD11b macrophage subsets while elderly individuals show no change in either macrophage subset. At 72h PE young subjects have 8 times more CD163 cells than CD11b cells (112) indicating that the predominant anti-inflammatory pool of macrophages before exercise is further augmented after exercise. Although both young and old at rest and post 72h after exercise show greater numbers of CD163 than CD11b macrophages, the older subjects have significantly fewer CD11b macrophages than younger subjects. This finding confirms that older individuals have a shift to the alternatively activated macrophage subset. Furthermore macrophage dysfunction is evident due to higher baseline levels of IL-1 β and IL-1RA and no increase in anti-inflammatory cytokines PE as younger subjects demonstrated (112). The findings indicate a perturbed macrophage response to resistance exercise in older individuals.

Summary. The response pattern of several leukocyte subsets including monocytes, neutrophils, CD19 B cells, CD4 and CD8 T cells as well as NK cells are all diminished in the elderly compared to the young showing the impact immunosenescence with age has on the immune response to resistance exercise. Although exercise may improve functionality of NK cells, the tissue remodeling process may be slower due to the observed impairment in macrophage numbers and function as well as the known deficits in neutrophil and monocyte functioning.

The Effects of Aging on Leukocyte Function

Decreased NKCA has been associated with poor lifestyle choices, illness and disease whereas maintenance of NKCA is associated with health and longevity in aging (16, 43, 74, 79, 94, 124).

Young. Although natural killer cell cytotoxic activity does not show resting differences based on training status, acute exercise attenuates NKCA later in recovery (102, 103). Immediately after exercise, no change in NKCA was determined despite a 225% increase in NK cells (103). However at 120 minutes PE NKCA decreased by 61% below baseline values when NK cells had decreased below baseline levels (103). NKCA does not appear to mirror changes in circulating NK cell numbers PE. Since the number of circulating NK cells does not appear to affect NKCA, it may be the subset of circulating NK cells that effect NKCA.

NK Cell Subsets. NK cells can be divided into two subsets based on the density of CD56 expression. CD56^{bright} NK cells compose ~10% of circulating NK cells while CD56^{dim} NK cells compose the remaining 90% (76). This distinction is important because of functional differences in these two NK cell subset populations. CD56^{bright} NK cells are more responsive to monokines (monocyte derived cytokines) and produce more cytokines while being less cytotoxic at rest (23, 24).

CD56^{dim} NK cells are more cytotoxic but produce less cytokines (23). The concomitant increase in CD56^{dim} NK cells and decrease in CD56^{bright} with aging may affect both the NKCA and cytokine regulatory capabilities of NK cells in the elderly.

Elderly. The variability of the NKCA response to exercise is a common motif in the literature and resistance training is no exception (39, 120, 131, 154). Resting NKCA has been shown to be unaffected by chronic training (118). The effects of acute and short term training are disparate. NKCA has shown both no changes and significant improvements after acute exercise and short-term training (39, 90). However, the significant improvements in NKCA were reported at all time points including baseline after short-term training. Seasonal variations may have caused or contributed to all the measured time points changing (53, 54, 97). Due to the variability in the NKCA response to resistance training in the elderly and only a single acute resistance training study performed in the young, it is difficult to make comparisons. In the elderly, there is either no change or an acute increase in NKCA after acute exercise (39, 90). In the young, there is no change until a decrease at 2h PE (103).

Lymphocyte Proliferation. Resistance exercise in young individuals has inconsistent effects on lymphocyte proliferation inducing either no effect, an increase or decrease (31, 91, 92, 103, 111). Lymphocyte proliferation consistently shows no response in the elderly possibly indicating a perturbed response to mitogenic signals in the elderly after resistance exercise (39, 115).

Catecholamines and the Immune Response to Resistance Exercise

Resistance Training and Catecholamines. Catecholamines have been shown to respond to a variety of acute resistance exercise programs and have demonstrated dependence on total work, rest period length between sets and reps, anticipation of exercise, training status and the level of metabolic stress (18, 36, 44, 51, 65, 68, 71). Training status does not affect the pattern of the catecholaminergic response but does affect the magnitude of the response (68). Catecholamines can affect blood flow regulation, cardiac contractility, the secretion of other hormones, substrate mobilization and the maintenance of force development (44, 66). Epinephrine and norepinephrine have been shown to increase above baseline values prior to exercise, during exercise and up to 5 minutes during the recovery period (36, 44, 68, 71). Some research indicates that norepinephrine may increase up to 15 minutes PE while epinephrine returns to baseline by this time point (18, 51). NK cells are also elevated during the same timeframe as catecholamines (31, 103, 116, 140). This has been demonstrated with adrenaline infusion, after the cessation of which, circulating NK cells decrease below baseline (126). The parallel increases in circulating catecholamines and NK cells after resistance exercise suggest that catecholamines are necessary to maintain NK cells in circulation and play a role in cellular adhesion.

Catecholamines and Cellular Adhesion. Catecholamines, specifically epinephrine, decrease cellular adhesion (10). Epinephrine infusion has been shown to mobilize cells but does not increase soluble adhesion molecules or alter the surface

expression of adhesion molecules such as VCAM-1, ICAM-1 or E-Selectin (4, 7, 8, 9, 126). Resistance exercise increases circulating catecholamines, but does not increase soluble adhesion molecules or alter surface expression (93, 108). However, resistance exercise does cause a redistribution of cells preferentially expressing specific adhesion molecules, namely, VLA-4 on lymphocytes and L-Selectin on neutrophils (93). The increase of lymphocytes expressing VLA-4 is due to an increase in circulating NK cells PE (93). NK cells are most likely preferentially recruited since they have the highest density of β_2 ADR (75). When catecholamines bind to β_2 ADR they cause an increase in cAMP and induce changes in cytoskeletal organization which may modify the adhesion of cells to endothelial walls (110, 128, 150). This may lead to the preferential redistribution of cells with specific adhesion molecule expression.

Although NK cells may be preferentially recruited to the circulation, NK cell subsets may not be equally redistributed. A recent review on NK cell subsets and acute exercise (endurance exercise) indicated that CD56^{dim} cells are preferentially redistributed into the circulation in greater magnitude than CD56^{bright} NK cells (144). This may be due to differences in adhesion molecule expression. It has been demonstrated that CD56^{bright} NK cells highly express CD62L (L-selectin), while CD56^{dim} cells express low levels of this adhesion molecule (45). Based on the research of Miles et al 1998 CD56^{bright} NK cells may not be preferentially recruited to the circulation due to their expression of L-Selectin. Therefore the RE literature may agree with the findings that CD56^{dim} cells are preferentially redistributed to the circulation, however further work on differences in VLA-4 expression on both NK cell subsets needs to be performed. Since neutrophils expressing L-Selectin were preferentially recruited, a combinatorial signal of hormone receptors and adhesion molecules unique to each cell subset may control their redistribution.

Cortisol and the Immune Response to Resistance Exercise

Introduction. Cortisol increases post resistance exercise especially bouts that utilize multiple sets with short rest periods between 60-120 sec (14, 17, 36, 88, 96, 148, 151). Plasma cortisol levels peak IP to 30 PE, then either remain elevated above baseline or begin to decline toward baseline 30-60 minutes PE (14, 69, 70, 96, 101, 116, 151). By 90-120 min PE cortisol either returns to baseline or decreases below it, followed by values below baseline at 4h PE (20, 61, 116). This timeline is important since neutrophils and monocytes have been shown to increase over this same time interval, and several studies have shown a relationship between changes in cortisol and leukocyte subsets after RE (20, 61, 87, 103, 116). Therefore it is important to clarify the effects of cortisol on leukocyte redistribution.

The Glucocorticoids and Leukocyte Subsets. Intravenous doses of cortisol have been used to isolate its effects on circulating leukocytes. However, this model is not reflective of the impact of cortisol after a bout of resistance exercise since other hormones with known effects on leukocyte adhesion are elevated in conjunction with cortisol PE. Cortisol administration induces neutrophilia between 1-2h

and 4-6h post injection and concomitantly induces lymphocytopenia and monocytopenia evident in the first hour and peaking 4-6h post injection (27, 37). After a bout of resistance exercise cortisol is correlated with increased neutrophil and monocyte counts, and decreases in CD8 T and NK cell counts (61, 103, 116). Although the relationship of neutrophils, lymphocytes and cortisol agree with cortisol administration studies, the directional relationship of cortisol and monocytes do not. There is evidence that cortisol can influence the transcription and therefore expression of adhesion molecules by endothelial cells suggesting a potential mechanism for the effects of cortisol on leukocyte adhesion (25). Since catecholamines which also increase post resistance training can influence the redistribution of cells with particular surface adhesion molecules it is plausible that some interaction effect between the influence of catecholamines and cortisol regulate the redistribution of monocytes. Similarly NK cells in the presence of elevated catecholamines early post exercise remain elevated, but after catecholamine levels decrease, cortisol becomes the dominant compartmentalizing factor. The ratio of these two hormones may be a crucial factor in determining the maintenance of leukocytes in the circulation.

Infiltration of Muscle Tissue by Leukocytes

Techniques Used to Quantify Leukocytes. Radiolabelling of leukocytes and muscle biopsies are the two techniques used to determine changes in muscle tissue accumulation and infiltration of leukocytes in humans. Radiolabelling of leukocytes is performed using Technetium-99m, a radionuclide tracer with a short half-life of 6h that restricts its use to a 24h period (28, 64). This short half-life leads researchers to forego a pre-exercise sample leading to comparisons of an exercised leg and a control leg (81, 106). Radiolabeling does not indicate muscle infiltration, but accumulation in a region whether it be adhesion to the walls of the microvasculature or penetration into the muscle tissue. Muscle samples obtained from biopsies are stained for leukocyte subsets to determine the magnitude of leukocyte infiltration (106, 112). However, the biopsy itself causes muscle damage leading to an inflammatory response (85).

Technetium 99m Measures. The general pattern of response is little to no increase in the accumulation of radiolabeled leukocytes during the first 4 to 8h PE followed by a significant increase above baseline 20-24h PE (81, 114). In an exception to this pattern, increased accumulation of radiolabeled leukocytes was seen in the quadriceps throughout the 24h PE period in a group of subjects which ranged from sedentary to physically active (106). The sedentary subjects showed markedly greater accumulation of ^{99m}Tc-labeled leukocytes in the quadriceps (106). Comparisons of the sedentary participants to the other more fit subjects demonstrates that training status can influence the timing and magnitude of leukocyte accumulation with sedentary subjects accumulating a greater number of leukocytes beginning sooner after the cessation of exercise.

Muscle Biopsy Measures of Tissue Infiltration. No significant increase in muscle infiltration is detected during the first 3h PE, but by 48h PE there is a significant increase in both neutrophil and monocyte/macrophage infiltration (84).

Muscle damage determined by Z-disk streaming followed the same response pattern as leukocyte tissue penetration showing no increase at 3h PE but a significant increase by 48h PE (84). This common response pattern suggests the timing of leukocyte infiltration coincides with the development of muscle tissue damage. In contrast, increased leukocyte infiltration of the muscle tissue has been observed at all PE time points (0.5 to 168h PE) with the greatest accumulation of leukocytes at 4 and 7 days PE (106). This response pattern may result from the inclusion of subjects with diverse training experience.

The Controversy of Infiltrating Neutrophils. Although neutrophils have been shown to extravasate into tissue during acute inflammation, it is controversial whether this occurs after a bout of resistance exercise (33, 135). Paulsen et al 2010 determined that the amount of neutrophil infiltration into the muscle tissue after exercise was minimal and instead proposed that the neutrophils accumulate in the microvasculature of the quadriceps by adhering to endothelial cell walls and that only a small percentage of these cells extravasated into the muscle tissue (106). In contrast to these findings Mahoney et al 2008 reported a 14-fold increase in the presence of neutrophils (84). The reason for these dichotomous results may be at least partially explained by the difference in methods used to detect neutrophils. Mahoney et al 2008 stained for MPO to distinguish neutrophils, but Paulsen et al 2010 did not explicitly label neutrophils (84, 106). Instead the number of CD68 cells (monocytes/macrophages) was subtracted from the number of CD16 cells (which by majority are neutrophils and monocytes/macrophages) to estimate the level of neutrophil infiltration (106). However, the indefinite findings concerning the amount of tissue infiltration by neutrophils is a common paradox in the literature of exercise induced muscle injury (127).

Location of Tissue Macrophages. Macrophages located in the skeletal muscle are known as histiocytes, which are macrophages found in connective tissue (95). Several studies have confirmed the location of macrophages in the connective tissue of muscle (106, 139). This appears to be the normal pattern seen where macrophages can surround a muscle fiber through habitation in the connective tissue, mainly the endomysium and perimysium (106, 139). However, macrophages have been shown to penetrate the muscle fiber itself if the muscle tissue becomes necrotic (106, 139). After exercise wider regions of endomysium and perimysium around muscle fibers have been observed, even areas where the ECM detached from the muscle fiber surface on one or more sides (139). Muscle fiber infiltration was not observed where muscle fibers were detached from the ECM (139) demonstrating the use of connective tissue by macrophages as a path to damaged muscle fibers.

Summary. Radionucleotide labeling of leukocytes and muscle biopsies confirm that muscle tissue accumulation and infiltration by leukocytes does not occur for the first 3h of recovery PE and perhaps up to 8h. Muscle tissue accumulation and infiltration have been demonstrated between 20-48h PE, but the resolution of tissue infiltration and inflammation is still controversial and most likely depends on a multitude of factors including the exercise program variables and the training

status of the individuals (Figure 1). Although evidence indicates tissue infiltration by monocytes/macrophages, the degree of infiltration by neutrophils is still debatable. Macrophages use the connective tissue system as roads to reach damaged muscle fibers, but if necrotic cells are present they will infiltrate the muscle cell itself.

Sex Differences

Introduction. Specific hormones that affect the immune system such as catecholamines and cortisol have been shown to respond differently to resistance exercise in men and women (72, 138). Sex differences in the extent of muscle damage after resistance exercise have been shown in studies using animal models but the effects of sex are mixed in humans (22). The purpose of this section is to highlight the sex differences in muscle damage and the endocrine system in response to resistance training and how these factors may affect the number of infiltrating leukocytes.

Endocrine Responses. There are many endocrine differences between sexes in the hormones that affect muscular adaptation to exercise and this information can be found elsewhere (72, 138). The hormones with the greatest effects on leukocyte redistribution are the primary focus here. The PE cortisol response after acute resistance exercise is mixed displaying either no sex difference or a greater increase during the PE recovery period in men (42, 72). No differences in the response pattern of norepinephrine have been demonstrated between sexes (41). Although the pattern of response for epinephrine is similar between men and women, men maintain higher epinephrine levels during the PE period than women (41).

Receptor Expression. Circulating leukocytes express several hormone receptors including β_2 ADR and GCR (41, 42). No significant sex differences in β_2 ADR have been observed for any leukocyte subsets. GCR has only been measured in B cells and demonstrated a greater density in men at baseline but not in respect to the PE response (42). Therefore, hormonal differences during the PE recovery period do not affect the temporal response pattern in GCR or β_2 ADR receptor density since it is similar between sexes. Since sex differences in hormone expression do not lead to altered receptor expression differential recruitment to muscle tissue may be independent of the influence of hormones and instead may be dependent on other signals.

Different Microenvironments: Muscle Damage. Some sex differences become apparent when determining the extent of muscle damage after exercise. No sex differences have been determined in the amount of muscle damage based on Z-disk streaming (141, 142). In contrast, the CK response shows either a greater response in men or that no differences exist. One study observed no differences in the CK response, although a trend existed for a lower response in women (141). In a second study men maintained a higher CK response for a more extended recovery period than women (142). However, the validity of using CK as a marker of muscle damage has been questioned (104). Sex differences in the CK

response may be due to the antioxidant effects of estradiol, but this effect is uncertain (5). Differences between sexes in the disruption of intracellular calcium concentrations within muscle fibers after exercise have been demonstrated in rats. After eccentric exercise, male rats demonstrated an increase in intracellular calcium concentration, that was significantly greater than female rats and ovariectomized female rats demonstrating an estrogen independent effect (137). Increased intracellular calcium in muscle cells is associated with muscle damage through several signaling pathways including activation of calpains and phospholipase A2 and increased production of reactive oxygen species (32, 48). The differences in calcium permeability in male and female muscle may explain differences in muscle damage.

Muscle Infiltration. Infiltration of muscle tissue by leukocytes and the level of tissue infiltration increases post resistance exercise (84, 106), but differences between sexes are less apparent. The day after a single bout of resistance exercise, men and women showed no differences in infiltration of neutrophils and macrophages by sex, but 24h after a 2nd repeated bout of resistance exercise women demonstrated significantly greater increases in neutrophils and macrophages than men (142). Increased muscle infiltration of neutrophils and macrophages has been observed 48h after a single bout of exercise, but only a trend was seen towards a greater increase in men than women (141). These studies indicate a sex difference in the timing of leukocyte infiltration leading to varying magnitudes of tissue infiltration at successive PE time points.

Summary. Although after resistance exercise sex differences exist in the levels of circulating hormones such as cortisol and epinephrine, there are no accompanying sex differences in the expression of β_2 ADR or GCR in circulating leukocyte subsets. No differences in the amount of Z-disk streaming are observed after a single bout of resistance exercise but women tend to display a lower CK response. Women may have a greater amount of leukocyte infiltration into muscle tissue than men, but this may be dependent on the timing of muscle biopsies and the level of ultra-structural damage and apoptotic cells. Differences in intracellular calcium accumulation between sexes may impact muscle damage or signaling between muscle fibers and leukocytes leading to differences in muscle tissue infiltration.

Effects of Resistance Training on Leukocyte Phenotypical Expression

Antigen Expression. Leukocytes express several receptors to aid in the response to environmental stimuli. CD64 and CD11b/CD18 are two such receptors that aid the cells in recognizing antibodies and components of the complement system respectively. CD11b/CD18 together compose the type 3 complement receptor. The CD11b/CD18 receptor is a glycoprotein found on the plasma membranes of neutrophils, monocytes and NK cells. It binds to the 3rd component of the complement system, iC3b, and results in phagocytosis of iC3b opsonized cells and causes adherence to vascular endothelium (26, 155). CD64 is the receptor for the Fc portion of IgG and is found on neutrophils and monocytes. Receptor binding causes antibody dependent cytotoxicity, phagocytosis, superoxide production and

degranulation (1, 130, 149). The changes in surface expression of these antigens after exercise is dichotomous hence no general response pattern can be discerned. The expression of CD11b and CD64 surface antigens have been shown to increase PE on neutrophils and monocytes after a single bout of exercise and to a greater extent than after a second repeated bout (109). In contrast, a single bout of exercise has demonstrated no significant changes in any of these surface antigens (125). Major differences between the studies that could cause the discrepancies were differences in subject training status and differences in the eccentric exercise protocol (109, 125).

TLR 4 and CD14 Expression. Toll-like receptor 4 is a pattern recognition receptor. CD14 is a co-receptor that aids TLR4 in the detection of lipopolysaccharide, a bacterial cell membrane component. They are highly expressed on monocytes and macrophages. TLR4 plays a role in the inflammatory response and chronic exercise has been demonstrated to provide anti-inflammatory effects. Changes in the expression pattern of TLR4 and CD14 in response to resistance exercise have been demonstrated in elderly women. TLR4 and CD14 surface expression were significantly greater in untrained subjects than trained subjects (40, 89). In corroboration of these findings TLR4 and CD14 mRNA expression were greater in untrained than in trained subjects (40). Dividing participants into HI and LO TLR4 expression groups has demonstrated that HI TLR4 expression coincides with greater expression of the LPS stimulated cytokines TNF- α , IL-6 and IL-1 β (89). Together these studies indicate that untrained subjects have higher TLR4 protein and mRNA expression than trained counterparts and that subjects who express higher levels of TLR4 also elicit a greater cytokine response to LPS stimulation. These findings show that chronic exercise may mediate some of its anti-inflammatory effects by affecting receptor expression for pathogen associated molecular patterns and by decreasing the cytokine response to stimulation. However, further research is required to determine if the decrease in TLR4 expression and subsequently lower cytokine secretion is beneficial in response to an actual infection.

Hypotheses and Future Directions

Initiation and Maintenance of the Cellular Innate Immune Response. It is plausible that the initiation of leukocyte infiltration into damaged muscular tissue may be due to recognition of intracellular components from the muscle such as desmin in combination with cytokines released from the muscle tissue itself (99, 143). These initial signals may activate/recruit resident macrophages to areas of damaged muscle tissue and induce the release of cytokines in cooperation with muscle cell myokines and satellite cells. The combination of cytokines can direct monocytes and neutrophils to damaged muscle tissue to aid in regeneration and repair. Maintenance of monocytes and neutrophils in the circulation to supply these cells to muscle tissue may be a function of CD56^{bright} NK cells. CD56^{bright} NK cells have been demonstrated to release several cytokines in response to co-stimulation of monokines such as IL-10, MIP-1 α , MIP-1 β , TNF- α , IFN- γ and GM-CSF (38). CD56^{bright} NK cells have also demonstrated the ability to produce G-CSF and M-CSF (123). Many of these cytokines promote a strong cellular

response acting as chemokines or activators for both macrophages and neutrophils as well as potential signals for hematopoietic release into the circulation of immature neutrophils and monocytes. CD56^{bright} NK cells may mediate tissue repair from a distance by supporting the actions of macrophages, neutrophils and monocytes but without direct interaction since these cells do not infiltrate damaged muscle tissue after acute resistance exercise (106).

Prevention of Self-Recognition Through Spatial Redistribution. Although intracellular proteins and cytokines may aid innate cells of the immune system to be directed to the damaged tissue to facilitate repair and regeneration, there is a potential hazard for self-recognition by the adaptive immune system. This may be why acute exercise doesn't redistribute T and B cells into the circulation to the same extent as the cells of the innate arm. Furthermore, lymphocytes are demonstrated to be sequestered into the lymphatic system in the intestinal area according to animal studies due to the effects of cortisol (145). The timing of distributing lymphocytes into the lymphatic system may be to sequester these cells out of the circulation and away from damaged muscle tissue where they may come into contact with intracellular debris. Furthermore, their distribution back into the marginated pool (or their location in secondary lymphoid organs) may also be timed for when antigen presenting cells or debris that have the potential to induce self-recognition may enter the lymphatic system, thereby maintaining a safety net against self-recognition through spatial separation by timing where the lymphocytes are distributed in the body after exercise.

Future Directions. The current literature has formed a foundation for the effects of resistance exercise on leukocyte redistribution. By studying the effects of each of the program variables on resistance exercise, a better understanding of the relationship between exercise and leukocyte redistribution can be obtained. To better understand the causes behind why each program variable induces leukocyte redistribution, additional research needs to be performed on surface adhesion molecule expression of all leukocyte subsets, how surface expression is affected by resistance exercise and what role hormones such as cortisol and catecholamines may play in redistribution and adhesion molecule expression. Only a single paper distinguishes NK cell subsets (118). Considering the functional differences of these cell subsets, their impact on health and how their proportions change with age, it is imperative to delineate the effects of exercise on these cell subsets. Finally, to better understand functional changes after resistance exercise, the application of -omics must be applied to resistance exercise research. The study of genomics in NK cell subsets determined several functional distinctions based on gene expression patterns (52). Expanding the application of genomics and proteomics to study functional differences in leukocyte subsets in response to exercise is a promising future step. Overall this paper has tried to summarize the current literature on resistance training and the immune response to condense the literature into a foundation. Based on this foundation and the suggestions for future research, a more coordinated multidirectional front of research can be pursued to better understand the impacts of resistance exercise on immune function.

Conclusion

After a bout of resistance exercise cells of the innate immune system, NK cells, monocytes and neutrophils are all preferentially elevated in the circulation PE, while cells of the adaptive immune system, the T cells and B cells, show a much lower magnitude of response. Changes in leukocyte redistribution generally follow a specific temporal pattern in young subjects. Monocytes and neutrophils aid in the repair and regeneration of muscle tissue as evidenced by their extravasation into muscle tissue or accumulation in the muscle vasculature. Increased circulating NK cells may function as supporting cells through cytokine mediation.

Elderly individuals display both an altered temporal pattern and magnitude of response for all leukocyte subsets. This disturbance is likely due to many factors including but not limited to immunosenescence, altered circadian rhythms, diminished catecholamine responses to acute resistance exercise, altered sensitivity to ACTH, and decreases in vascular plasticity. Although not all of the humoral and immune perturbations associated with aging can be restored through exercise, resistance training has the potential to improve the natural killer cell response to acute exercise, improve vasodilation and potentially shear stress stimulated leukocyte redistribution into circulation. Exercise alone may not restore leukocyte functionality, but the use of resistance exercise to study alterations to leukocyte function with age may shed light on new means to combat immunosenescence with aging.

Resistance training program variables such as rest interval length and load can impact the magnitude of leukocytosis after exercise. But further research needs to be done to determine the effects of each program variable independently. By understanding the impact each exercise program variable has on leukocyte redistribution, phenotype and function, a more optimal exercise prescription could be made. A more targeted exercise prescription that considers the effects on the immune system could be used to improve or maintain athletic performance during competition, and could be beneficial to health maintenance with age and the perturbation of disease.

Determining the potential therapeutic impact of resistance exercise on chronic illness is another important area of research, but it has received little attention (115). Although the study of resistance training and immunology is an important area of research on its own, studying the intersection of immunology and muscle physiology could also extend insight into the areas of sterile inflammation, muscular diseases and even autoimmune diseases. Resistance exercise provides a useful model for understanding how the immune system interacts with damaged and healthy tissue and how leukocyte redistribution is controlled.

Table 1. Summary of study designs and acute resistance exercise testing details of the research on leukocyte response patterns and resistance exercise.

Young Acute			Acute Testing Details							
First Author	Second Author	Year	Gender	Age	Groups	SetsxReps	Load	Rest	Type	Exercises
Ramel A	Wagner KH	2003	Male	29.5 ± 7.1	TR vs NRT	2 sets	75% 1RM	1 min	Circuit	Bench Press, Leg Press, Lat Pulldown, Leg Extension, Shoulder Press, Triceps, Crunch, Vertical Row, Biceps Curls and Pullups
Ramel A	Wagner KH	2004	Male	29.5 ± 7.1	TR vs NRT	1 set	75% 1RM	1 min	Circuit	Bench Press, Leg Press, Lat Pulldown, Leg Extension, Shoulder Press, Triceps, Crunch Vertical Row, Biceps Curls and Pullups
Nieman DC	Henson DA	1995	Male	24.9 ± 1.2	TR	8x10	65% 1RM	3 min	Lower Body	Squat
Mayhew DL	Thyfault JP	2005	Male	22.2 ± 0.3	1 min vs 3 min rest	10x10	65% 1RM	1/3 min	Lower Body	Leg Press
Miles MP	Leach SK	1998	Female	18-35	NRT	6x10	75% 1RM	2 min	ARET	Squat
Petridou A	Chatziniolaou A	2007	Male	L: 23.8 ± 1.1 O: 24.2 ± 1.0	Lean vs Obese	3x10-12	70-75% 1RM	2 min	Total Body	Chest Press, Seated Row, Leg Press, Shoulder Press, Leg Extension, Leg Curl, Biceps Curs, Triceps Extension, Ab Curls, Back Extension
Dohi K	Mastro AM	2001	Female	HI: 23.6 ± 2.6 LO: 21.4 ± 3.5	HI vs Lo Strength	6x10	10RM	2 min	ARET	Squat
Nieman DC	Henson DA	1994	Male	TR: 23.6 ± 0.7 NRT: 22.4 ± 0.5	TR vs NRT	1 RM squat testing	1RM	NR	Lower Body	Squat
Potteiger JA	Chan MA	2001	Female	TR: 22.8 ± 1.6 NRT: 22.9 ± 0.9	TR vs NRT	3x10	10RM	3 min	Total Body	Leg Press, Bench Press, Leg Extension, Overhead shoulder Press, Seated Row, Leg Curls, Biceps Curls
Stoek C	Schaller K	1995	Male	22-29	NRT	3 sets	70% by Reps	NR	Circuit	5 different exercises
Kraemer WJ	Clemson A	1996	Male	26.9 ± 4.8	HI vs Lo Cortisol	8x10	10RM	1/3 min	Lower Body	Squat
Miles MP	Naukam RJ	1999	Female	21-36	HI CK vs Lo CK	Arm Curls: 2x25	Maximal	5 min	Eccentric	Leg Curls and Arm Curls
Simonson SR	Jackson CGR	2004	Male	30 ± 7	TR and NRT RT vs Con	Leg Curls: 3x20 3x8-10	60°/sec	1,2, W/R	Total Body	Crunches, Chest Press, Pulldown, Leg Curls, Leg Extension, Leg Press, Seated Rows and Shoulder Press
Pizza FX	Davis BH	1996	Male	20-37	NRT	Arm Curls: 25	NR	None	Eccentric	Arm Curls
Saxton JM	Claxton D	2003	NR	20-37	TR	Quadriceps: 2x25 Triceps: 2x25	1.05 rad/sec 0.35 rad/sec	5 min 5 min	Eccentric	Leg Extensions and Triceps Extensions
Stupka N	Tarnopolosky MA	2001	Male & Female	22 ± 2 23 ± 2	NRT	Bench Stepping Leg Press: 3x12 Leg Ext: 10x10	20 steps/min 120%	None 3 min	Bench Step Eccentric	Bench Stepping for 40 minutes Leg Press and Leg Extension

Stupka N	Lowther S	2000	Male & Female	22.75 ± 2.4 22.1 ± 2	NRT	Leg Press: 3x12 Leg Ext: 9x12	120% Concentric 1RM	1 min/set every 3rd set 3 min	Eccentric	Leg Press and Leg Extension
Fragala MS	Kraemer WJ	2010	Male & Female	24.63 ± 5.07 22.13 ± 3.09	Male vs Female Exercise vs Control	6x5	90% 1RM	3 min	Lower Body	Squat
Fragala MS	Kraemer WJ	2011	Male & Female	24.63 ± 5.07 22.13 ± 3.09	Male vs Female Exercise vs Control	6x5	90% 1RM	3 min	Lower Body	Squat
MacIntyre DL	Reid DW	1996	Female	20-33	Exercise Leg vs Control Leg	30x10	Maximal	20 sec	Eccentric	Leg Extensions
Paulsen G	Cameri R	2010	Male	28 ± 4	Exercise Leg vs Control Leg	30x10	30°/sec Maximal	30 sec	Eccentric	Leg Extensions
Raastad T	Risoy BA	2003	Male	27.2 ± 2.7	Exercise Leg vs Control Leg	Leg Press: 5x3 Leg Ext: 5x6	30°/sec 100% 3RM 100% 6RM	3 min	Lower Body	Leg Press and Leg Extension
Mahoney DJ	Safdar A	2008	Male	23.4 ± 3.7	NRT	30x10	Maximal	1 min	Eccentric	Leg Extensions
Young Chronic										
Miles MP	Kraemer WJ	2002	Female	18-30	Strength & Power TB Strength & Power UB Strength & Hyper TB Strength & Hyper UB Non-exercise Con	No Acute Testing				
Miles MP	Kraemer WJ	2003	Female	18-30	TB vs UB	6x10	75% 1RM	2 min	ARET	Squat
Supplementation										
Carlson LA	Headley S	2008	Male	21.1 ± 1.4 21.0 ± 2.2	CHO vs Placebo	4x10	55/65% 1RM	1 min	Total Body	Leg Press, Lat pulldown, Bench Press and Leg Curls
Nieman DC	Davis JM	2004	Male	19- 27	CHO vs Placebo	4x10	1:40% 1RM 3:60% 1RM	2 min for UB 3 min for LB	Total Body	Flat Bench Press, Incline Bench Press, Military Press, Upright Row, Bentover Bar Row, French Curl, Biceps Curl, Back Squat, Front Squat and Deadlift.
Koch AJ	Pottenger JA	2001	Male	25 ± 2.8	CHO vs Placebo	5x10 3x10	65% 1RM 85% 1RM		Lower Body	Squat Half Squat
Hulmi JJ	Myllymaki T	2010	Male	23.9 ± 2.0	Whey vs Placebo Study I: Young, TR	5x1 3x10 4x10	1RM 10RM 1RM	3 min 3 min 2 min	Lower Body	Squat Squat Leg Press
Hulmi JJ	Myllymaki T	2010	Male	Y: 22-26 O: 57-65	Whey vs Placebo Study II: NRT Young and Old	5x10	10RM	2 min		Leg Press

		Young Chronic														
Machado M	Koch AJ	2010	Male	18.4 ± 0.8	Caffeine vs Placebo	3x10	10RM	2 min	Total Body	Bench Press, Pullover, Biceps Curfs, Triceps Extensions, Leg Extensions and Prone Leg Curfs						
Kawada S	Kobayashi K	2010	Male	22.8 ± 4.0	Cystine/Theanine vs Placebo	4-6 sets, 6-10 reps	>80% 1RM	NR	NR	3-5 Free weight exercises 1st week: 3 sessions 2nd week: 6 sessions						
		Elderly Acute														
Przybyla B	Gurely C	2006	Male	Y: 31.9 ± 7.1 O: 71.4 ± 4.6	Young vs Old NRT Males	3x8 3rd set to failure	80% 1RM	2 min/set	Lower Body	Leg Press, Leg Curl and Leg Extension						
Neves SC	Lima RM	2009	Female	67.5 ± 3.9	S50% S80% SC: Control	2x13 2x8 no exercise	50% 1RM 80% 1RM	80 sec	Total Body	Bench Press, Lat Pulldown, Seated Row, Leg Extension, Leg Curl and Leg Press (equated work volume)						
		Elderly Chronic														
Rall LC	Roubenoff R	1996	Male & Female	Y: 25.8 ± 2.5 O: 70.3 ± 5.0 Con: 68.8 ± 2.9	Young Old RT Old Control	3x8	80% 1RM	2 min	Total Body	Abdominal, Back Extension, Chest Press, Leg Press and Leg Extension						
Bermon S	Philip P	1999	Male & Female	67-80	Old RT Old Control Young Control	3x8	80% 1RM	2 min	Total Body	Leg Press, Knee Extension and Seated Chest Press						
Bermon S	Philip P	2001	Male & Female	Y: 29.4 ± 0.4 O: 70.1 ± 1.0	Old vs Young	2x12 4x5	12RM 5RM	2 min	Total Body	Leg Press, Chest Press and Leg Extension						
McFarlin BK	Flynn MG	2005	Female	RT: 71.8 ± 6.5 C: 73.1 ± 6.0	RT vs Con	2x8 @ 80% 1RM 3rd set to failure	80% 1RM	NR	Total Body	Seated Leg Press, Knee Extension, Knee Flexion, Seated Chest Press, Chest Flys, Lat Pulldown, Shoulder Press, Seated Rows, hip abduction and hip adduction						
Raso V	Benard G	2007	Female	60-77	Con vs RT	No Acute Testing			Lower Body	Leg extension, Leg Curl, Plantar Flexion and Dorsiflexion						
Flynn MG	Fahlman M	1999	Female	RT: 72.6 ± 3.5 C: 72.9 ± 4.9	RT vs Con	2x8 3rd set to failure	80% 1RM	NR	Lower Body	Leg Abduction, Leg Adduction, Hip Extension and Hip Flexion						

Author	Year	Sex	Age	Pre vs Post	3x8	80% 1RM	NR	Total Body	Exercises
Bobeuf F	2009	Male & Female	61-73		3x8		NR	Total Body	8 exercises for upper and lower body
Flynn MG	2003	Female	65-85	HRT NHR MB Control	2x8 3rd set to failure	80% 1RM	1.5 min	Total Body	Seated Leg Press, Knee Extension, Knee Flexion, Upright Chest Press, Chest "fllys", Lat Pulldown, Shoulder Press, Upright Row, Hip Abduction and Hip Adduction
McFarlin BK	2004	Female	TR: 67 ± 5 NRT: 69 ± 5	TR vs NRT Hi TLR4 vs Lo TLR4	NR	NR	NR	Total Body	Seated Chest Press, Chest Fly, lat Pulldown, Hip Abduction, Hip Adduction, Seated Row, Knee Extension, Knee Flexion and Seated Leg Press

Abbreviations: TR = Trained, NRT = Not Resistance Trained, RT = Resistance Training, Con = Control, TB = Total Body, UB = Upper Body, LB = Lower Body, CK = Creatine Kinase, WR = Work:Rest Ratio, TLR4 = Toll-Like Receptor 4, HRT = Hormone Replacement Therapy, NHR = No Hormone Replacement Therapy, MIB = No hormones but on medications that could influence bone, CHO = Carbohydrate, HI = High, Lo = Low, ARET = Acute Resistance Exercise Test, NR = Not Recorded (to indicate that the descriptor was not mentioned in the text)

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