Exercise and the Regulation of Inflammatory Responses

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CHAPTER FOURTEEN

Exercise and the Regulation of Inflammatory Responses

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Contents

Abstract

Exercise initiates a cascade of inflammatory events, which ultimately lead to long-term effects on human health. During and after acute exercise in skeletal muscle, interactions between immune cells, cytokines, and other intracellular components, create an inflammatory milieu responsible for the recovery and adaption from an exercise bout. In the systemic circulation, cytokines released from muscle (myokines) mediate metabolic and inflammatory processes. Moderate exercise training results in improvements in systemic inflammation, evident by reductions in acute phase proteins. The anti-inflammatory effects of regular exercise include actions dependent and independent of changes in adipose tissue mass. Future research should encompass approaches, which attempt to integrate other, less-recognized physiological processes with acute and long-term inflammatory changes. This will include investigation into metabolic, endocrine, and immune components of various tissues and organs.

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ABBREVIATIONS

CRP C-reactive protein
GPx glutathione peroxidase
IL interleukin
IL-10 interleukin-10
IL-1β interleukin-1 beta
ROS reactive oxygen species
SOD superoxide dismutase
TLR toll-like receptor
TNF-α tumor necrosis factor-alpha

1. A BRIEF HISTORY OF INFLAMMATION AND ITS UNDERLYING RELATIONSHIP TO EXERCISE

In the first century medical encyclopedia, *De Medicina*, the Roman physician Conrelius Celsus first introduced four cardinals signs of inflammation, "*Rubor et tumor cum colore et dolore*"; or "redness and swelling with heat and pain." Nearly two millennia later, in the mid-1800s, Rudolf Virchow introduced the fifth cardinal sign of inflammation, "*function laesa*"; or "loss of function," which described the inadequate functionality of cells when exposed to a stressful stimuli.[1] Virchow proposed that these five characteristics are a product of a larger inflammatory process that combats "cellular" stress. These insights by Virchow broke sharply away from the traditional view of "humor imbalance" as the mediator of health and sickness, and thus helped usher in a new investigative era into inflammatory processes.[1] Building on the work of Virchow and others, Eli Metchnikoff, in 1892, proposed that inflammatory responses are not only vital for host defense but also imperative for natural tissue homeostasis.[2] Importantly, Metchnikoff suggested that the innate immune system (i.e., macrophages and neutrophils) might induce a broad range of remodeling processes, which are not necessarily detrimental to a host organism.[1,2] Following this, and just before the turn of the nineteenth century, Robert Koch and Louis Pasteur proposed the germ theory of diseases, a vital step for understanding microbes as major inducers of acute inflammation.[1]

Over a century after Koch and Pasteur, a far more expansive understanding of the underlying inflammatory processes of health and disease has been revealed. Presently, inflammation is recognized as "a perpetual and essential immune response that maintains tissue homeostasis under a variety of noxious conditions."[1] Inflammatory process can be separated into four

distinct components: inducers, sensors, mediators, and targets.[1] Together, various combinations of these components invoke inflammation that is vital for host defense from pathogens as well as repair from other internal disturbances. Unfortunately, the necessity of the inflammatory insult to combat such conditions may, paradoxically, lead to negative consequences within an organism. More specifically, chronic low-grade inflammation disrupts tissue homeostasis in ways that drive the progression of chronic conditions, such as diabetes, atherosclerosis, autoimmune diseases, and cancer.[3] With such devastating consequences, researchers and physicians have and will continue to search for ways to combat such chronic inflammatory insults.

Promisingly, a potent and long-lasting anti-inflammatory therapy exists in the form of physical exercise. This is supported by a vast number of epidemiological studies, which show that the long-term exercise training and/or increased physical activity greatly reduce the occurrence of chronic inflammatory diseases.[3–5] Interestingly, however, exercise only exerts its anti-inflammatory effect after an intricate and time-dependent inflammatory cascade that begins with largely proinflammatory actions. Such acute inflammatory actions, if not resolved, may lead to immunosuppression and long-term pathologies in chronic exercisers (i.e., upper respiratory tract infections).[6,7] In light of these variable effects, accounting for intensity, duration, and recovery from exercise is key to understanding the time course and resolution of the inflammatory response.

To help address how exercise regulates inflammation, this chapter will aim to unravel both the molecular mechanisms and systemic inflammatory effects of both acute and long-term exercise training. We will begin by discussing the timeline of acute, inflammatory actions within the primary tissue that responds to exercise skeletal muscle. Next, we will explore the acute, systemic inflammatory effects of acute exercise. Throughout this section, readers will also be exposed to the major inflammatory regulators (i.e., cytokines), as well as the possible sources and mechanisms which regulate systemic inflammation. In Section 2 of this chapter, we will explore effects of long-term exercise training on inflammatory processes. Here, we will also aim to unravel the roles of exercise in regulating inflammation in tissues and organ systems outside of skeletal muscle, including adipose tissue; a well-established inflammatory mediator. Throughout all sections of this chapter, we will include evidence from both humans and animal models, which together will help integrate mechanistic data with clinical applications of exercise training.

2. EXERCISE AND ACUTE INFLAMMATION IN SKELETAL MUSCLE

Muscular contraction is required for locomotion in mammals, thus skeletal muscle seems the most appropriate tissue to begin the investigation into the inflammatory processes regulated by exercise. This section will discuss the roles of metabolic and muscular injury by-products in inducing inflammatory events within skeletal muscle during and after acute exercise. We will also explore possible mechanisms by which inflammatory processes initiate long-term adaptation within skeletal muscles.

A large portion of exercise-induced inflammation within the muscle can be traced to mitochondrial uncoupling and the subsequent induction of reactive oxygen species (ROS). Such accumulation results in numerous downstream affects within the myocyte (muscle cell) and the surrounding tissue.[8] Namely, exercise-induced ROS generation may initiate a series of redox-sensitive intracellular signaling events. For example, NF-kappaB (NFkB) and activator protein-1 (AP-1), both potent transcription factors involved in inflammation, are activated after exhaustive exercise.[9] The relationship between exercise-induced ROS and these transcription factors became apparent when a potent xanthine oxidase inhibitor, allopurinol, was sufficient to attenuate NFkB binding in rat skeletal muscle.[10] Other proteins linked to inflammatory processes after exercise include the family of stress-activated mitogen-activated protein kinases (MAPKs), which together initiate processes important for inflammation, muscular adaptation, and metabolic control within skeletal muscle.[11,12] Interestingly, the MAPK family (p38, erk 1/2, jnk, and erk 5) are differentially activated depending on the exercise modality.[10,13] For example, it appears that concentric exercise induces phosphorylation of $MAPK^{erk\ 1/2}$ but not $MAPK^{p38}$. On the other hand, eccentric exercise can concurrently activate both kinases, leading to separate downstream signaling events.[14]

The differentially activated MAPK pathways highlight the complexity of muscular pathways and the subsequent inflammatory processes that ensues after exercise. These pleiotropic effects are highly dependent on the mode of muscular contractions (eccentric vs. concentric) as well as the intensity, the duration, and the novelty of an exercise task. In addition to the production of ROS, these factors also contribute to the degree of muscle damage after exercise. Current knowledge indicates that muscle damage is initiated when myofibrils are stretched during contraction.[8] An immediate response

to muscle injury is the release of a vast array of damage-associated molecular patterns (DAMPs), which are released into the extracellular environment in response to trauma.[15] The result is integrity disruption within the myocyte, which includes disturbances in the sarcoplasmic reticulum, transverse tubules, and myofibrillar proteins.[8,16] Excessive damage to these areas can lead to alterations in calcium homeostasis and subsequent proteolytic or inflammatory events.[8] Damage to proteins and membranes within these areas also result in an increase in inflammatory agents such as prostaglandins, substance P, and inflammatory cytokines, which promote the migration of innate immune effectors (i.e., macrophages and neutrophils) to the damaged area.[17–19]

3. THE RESOLUTION OF INFLAMMATION WITHIN SKELETAL MUSCLE: A COORDINATED INFLAMMATORY RESPONSE

The promotion of ROS and DAMPs by exercise can and has been viewed as a deleterious response. However, there is growing evidence that many of the pro-oxidative and proinflammatory processes that occur after acute exercise may be vital for the long-term adaptive responses to exercise training.[8] The temporal regulation of antioxidant enzymes and anti-inflammatory agents, which initiate metabolic adaptation and tissue repair within skeletal muscle, is evidence of such a phenomenon. The adaptive responses within skeletal muscle are modulated partially by antioxidant enzymes and innate immune cells, mainly neutrophils and macrophages, which produce a pattern of signals involved in satellite cell activation, matrix remodeling, and neovasculature formation.[20]

Despite their negative connotation, ROS are important for the induction of endogenous antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase within skeletal muscle and other tissues. Such antioxidant enzymes serve many protective functions within the myocyte and other tissues.[8] For example, reduced glutathione acts as an electron donor and engages various biological roles, which include the detoxification of electrophilic xenobiotics and the modulation of redox-sensitive pathways.[21] These antioxidant pathways also lead to reduction in proinflammatory cytokines (i.e., tumor necrosis factor-alpha (TNF-α)) produced by skeletal muscle or the associated immune cells.[22]

The exercise-induced proinflammatory response and subsequent immune cell recruitment and polarization may also be required for repair

and adaptive processes within skeletal muscle. Evidence of this stems from studies showing that the nonsteroidal anti-inflammatory drugs disrupt both the early translational responses within skeletal muscle[23]and the resolving lipid mediator response.[24] A dynamic, time-dependent polarization of macrophages during the tissue repair process further exemplifies the importance of the initial inflammatory response to exercise. A switch from an initial M1 proinflammatory phenotype 24 h after eccentric exercise, to an M2, anti-inflammatory phenotype 48–72-h after exercise, characterizes this phenomenon.[25] It is hypothesized that the initial recruitment of M1 macrophages is vital for the phagocytosis of necrotic cells as well as the proliferation of myogenic cells.[15,25] The effector molecules (i.e., ROS and Reactive Nitrogen Species (RNS)) and inflammatory cytokines (interleukin-1 beta (IL-1β), TNF-α, and IL-6) produced by M1 macrophages are the most likely candidates that promote necrotizing and inflammatory processes.[25]

The subsequent induction of M2 macrophages is perhaps the least understood of the inflammatory processes after exercise, but nevertheless is vital for muscle repair and regeneration. Namely, muscle recovery is largely dependent on the MAP kinase phosphatase-1 (MKP-1), which promotes p38 MAPK downregulation in macrophages, and subsequently promotes M1 to M2 macrophage differentiation.[26] Additionally, AMP-activated protein kinase (AMPK) alpha1 and cAMP response element-binding protein may also play integral roles in macrophage phenotype switching during muscle regeneration.[27] More recently, a unique population of T-regulatory cells has also been shown to be a key component to muscle repair and regeneration. More specifically, there may exist a "muscle-specific" T-regulatory cell population which is located in close proximity to regenerating satellite cells, exhibits anti-inflammatory and regenerative properties (IL-10 and TGF-β), and produces growth factors (i.e., Amphiregulin) that regulate myocyte regeneration.[28]

4. BEYOND THE MUSCLE: ACUTE EXERCISE AND SYSTEMIC INFLAMMATION

Acute exercise can also induce changes in the inflammatory milieu in areas beyond the skeletal muscle. Massive changes in circulating cytokines (although interestingly not the prototypical proinflammatory cytokines TNF-α and IL-1β) after acute exercise are evidence of this. Notably, some of these cytokines are postulated to be released directly from skeletal muscle, and thus have been termed "myokines."[29] In addition to proposed metabolic effects,[30] one particular myokine, IL-6, has pleiotropic effects on systemic

immune function.[31] More specifically, IL-6 initiates the release of anti-inflammatory cytokines such as IL-1 receptor antagonist (IL-1RA) and IL-10.[32] IL-1RA binds to the IL-1 receptor (IL-1R), which inhibits the potent and deleterious effects of proinflammatory cytokines, IL-1β and IL-1α.[33] Meanwhile, IL-10 exerts anti-inflammatory effects on a variety of immune cells including reducing the expression of Major Histocompatibility Protein (MHC) molecules, cell adhesion molecules, and costimulatory molecules (CD80 and CD86) on antigen-presenting cells.[33,34] IL-10 also downregulates proinflammatory cytokines, T cells, and other effector cells, thereby limiting the capacity of these cells to maintain a prolonged inflammatory response.[34]

The anti-inflammatory effects of IL-6 were clearly demonstrated when a recombinant version of the cytokine (infused at levels observed during exercise) initiated a subsequent increase in circulating IL-1RA, IL-10, and cortisol levels.[35] However, the precise mechanisms of how exercise-induced release of IL-6 leads to anti-inflammatory cytokine production are still unclear. One prevailing theory is that exercise-induced IL-6 initiates production of IL-1RA through peripheral blood mononuclear cells and/or resident tissue macrophages.[33] Regardless of the mechanism, the acute and potent induction of anti-inflammatory cytokines after exercise has profound effects on inflammation and immune function.

The inflammatory response following an exercise bout may also initiate proinflammatory and cell death responses within immune cells and effected tissue, but this largely depends on the modality and the intensity of the exercise.[36] Examples of these phenomena have been demonstrated in humans and rodents, and likely involve numerous mechanisms. One example of such a response was shown by an increase in circulating IL-17 and IL-23 after an intensive endurance exercise event.[37] Briefly, IL-17 and IL-23 represent active components of the TH17 axis and have numerous inflammatory effects on various tissues. IL-17 is the major proinflammatory effector of TH17 cells, and IL-23 promotes the differentiation to an IL-17 producing TH17 phenotype.[38] A postulated mechanism by which IL-17 may initiate an inflammatory response is through activation and recruitment of neutrophils through the chemokine IL-8.[37] Perhaps not surprisingly then, IL-17 and IL-23 production after exercise were strongly correlated with neutrophil activation marker myeloperoxidase, and muscle damage marker myoglobin (Mb), indicating a possible role of these cytokines in regulating neutrophil activation and subsequently muscle damage.[37] The source and cause of IL-17 and IL-23 release after exercise is less understood, but may be linked to IL-6 production.

Systemic inflammation after exercise may also be dependent on other unique events that occur after exercise. Notably, researchers have linked intense, prolonged exercise with an increase in circulating lipopolysaccharide (LPS), a major component of the outer membrane of Gram-negative bacteria.[39,40] Termed "endotoxemia," the release of enteric Gram-negative bacteria and/or its associated cell membrane components ultimately leads to a systemic inflammatory response through activation of pattern-recognition receptors (PRRs) on various cell types.[41] The release of enteric bacteria into circulation has been linked to a loss of barrier integrity in the gastrointestinal tract (GI) partially caused by aberrant function or activity of the epithelial cytoskeleton, tight junction proteins (TJPs), and/or Paneth cells.[42–44] The disruption in the epithelial barrier is likely a result of splanchnic hypoperfusion, a conserved evolutionary adaptation to enhance blood perfusion to tissues required for movement and respiration.[42]

The regulation of inflammation and immune trafficking within the GI after exercise may also be traced to local host–microbe interactions. For instance, Uchida *et al*. showed that the administration of the bacterial protein flagellin (FG) after exhaustive treadmill exercise exacerbated systemic inflammation in mice as measured by circulating TNF-α.[45] Moreover, these authors found that the inflammatory response may be exacerbated by the catecholamine, epinephrine, through an upregulation of the bacterial FG receptor, toll-like receptor 5 (TLR-5), on GI epithelial tissue.[45] Together, these data suggest that the GI tract and associated immune tissue may be especially sensitive to GI barrier disruption during and after acute exercise, as intraluminal bacteria exposed to epithelial cells and immune cells can induce an exacerbated inflammatory response. Despite this, data regarding the regulation of inflammation by enteric microbes during and after acute exercise are still lacking.

Despite the increases in circulating endotoxin and inflammatory cytokines that can occur after strenuous exercise, the acute immunosuppressive effects of exercise are still quite significant. Starkie *et al*. first demonstrated such an effect by showing that a single endurance exercise bout significantly reduced endotoxin-induced TNF-α production in humans.[46] A likely mechanism behind this blunted inflammatory response may be a result of alterations in PRRs on innate immune cells. Indeed, Lancaster *et al*. demonstrated a significant decrease in TLR (1, 2, and 4) receptor expression on circulating monocytes 1.5 h after intensive endurance exercise.[47] This finding was later confirmed by others.[48,49] Unfortunately, the mechanisms regulating TLR expression on circulating leukocytes after exercise are still not

well understood, but may be related to core body temperature, stress hormones, anti-inflammatory cytokines, and/or heat shock proteins.[50]

As discussed briefly in the previous sections, circulating hormones have significant effects on the inflammatory process after exercise. The most studied of these hormones are catecholamines (epinephrine and norepinephrine) and glucocorticoids (cortisol), likely due their relative ease of manipulation and well-defined actions on the immune system. These hormones are substantially increased after exercise by activation of the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis in dose- and time-dependent fashions. Cortisol (the major glucocorticoid in humans) can induce genomic and nongenomic anti-inflammatory effects, thus reducing the production of major inflammatory cytokines.[51,52] Catecholamines serve a parallel anti-inflammatory action by downregulating the production of inflammatory cytokines from circulating leukocytes.[53] However, as previously discussed, catecholamines may have direct or indirect pro-inflammatory actions within other areas of the body, most notably the GI tract.[45]

5. SUMMARY OF ACUTE EXERCISE AND INFLAMMATION

In summary, an acute exercise bout initiates a complex, time-dependent cascade of inflammatory events, which depends largely on the mode, intensity, duration, and familiarity of the exercise bout (Fig. 1). The inflammatory mediators which regulate this response act upon various tissues, most notably the skeletal muscle. Here, the inflammatory cascade is characterized by an initial proinflammatory response (~1.5–24 h after exercise) which is followed by an anti-inflammatory muscle regenerative response (~24–72 h after exercise). Acute exercise also initiates "inflammatory" processes in the circulation, evident by significant rises in circulating myokines (i.e., IL-6) followed by a subsequent increase in circulating anti-inflammatory cytokines (IL-10 and IL-1RA). Acute exercise also acts on immune cell receptor presentation, evidenced by a significant reduction of TLRs on circulating monocytes 1.5 h after strenuous exercise. It is currently unclear how an acute inflammatory response to exercise initiates long-term adaptive responses. Nevertheless, it is plausible that the acute anti-inflammatory processes of exercise may propagate into some of the well-known beneficial effects of exercise training, which will be discussed in the section 6.

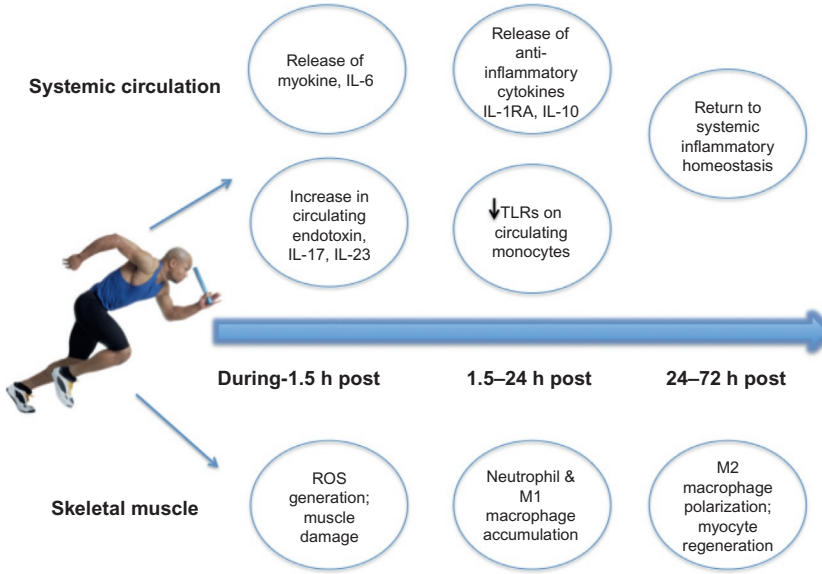

Figure 1 The effects of acute exercise on skeletal muscle and systemic inflammation. *Abbreviations*: IL, interleukin; ROS, reactive oxygen species; TLR, toll-like receptor; ra, receptor antagonist.

6. EXERCISE TRAINING AND CHRONIC INFLAMMATION

Studies have demonstrated that chronic inflammation may increase the risk of disability and mortality even in people who do not have clinical disease.[5] For instance, for individuals with infection, C-reactive protein (CRP) levels may be 1000-fold higher than the standard values.[54] CRP is a hepatic acute phase protein that is commonly used as a biomarker of systemic inflammation and risk factor for cardiovascular disease (CVD) if levels are >3 mg/L[55] and, importantly, its levels have been correlated with frailty, morbidity, and mortality.[56,57] Ridker *et al.* have shown that the CRP levels predict CVD effectively in middle-aged and older population.[58,59] In addition, increased CRP is related to diabetes,[60] heart failure,[61] physical disability,[62] and other diseases. Therefore, studying ways of diminishing chronic inflammation is critical for reducing the risk of inflammation-associated diseases.

Regular physical activity has the potential to improve chronic inflammation.[63] A large number of cross-sectional studies have consistently reported an inverse association between self-reported physical activities or objectively

measured aerobic capacity with inflammatory blood biomarkers.[64] More definitive evidence comes from intervention studies. Regular moderate exercise training has been shown to act in an anti-inflammatory fashion in a number of states where inflammation is chronic in nature including aging,[65] obesity,[66] metabolic disease,[67] spinal cord injury,[68] and stroke[69] among others. For example, we found that 10 months of cardiovascular exercise training significantly reduce serum CRP in a cohort of community-dwelling older adults.[70] Many,[70–72,61,73] but not all,[74,75] intervention studies have demonstrated reduced inflammatory biomarkers. The evidence seems to indicate that if the exercise intervention is of long enough duration (>3 months) and of sufficient intensity then reductions in inflammatory biomarkers will be realized. Moreover, exercise-induced reductions in inflammation seem to occur at a higher rate in studies that have utilized participants with elevated inflammatory markers to start with (e.g., obese, aged, and diabetic).

7. POTENTIAL MECHANISMS OF THE EFFECT OF EXERCISE TRAINING ON ANTI-INFLAMMATION

While the measurement of blood inflammatory biomarkers in people is informative, they do not shed light on tissue-specific inflammation or its causes. This is important because local tissue inflammation results in an increase in blood inflammatory biomarkers. Animal models assist in localizing inflammatory defects to particular tissues of interest and will aid in the identification of tissue-specific anti-inflammatory mechanisms associated with regular exercise. There are several potential mechanisms (Fig. 2), whereby regularly performed exercise may dampen chronic inflammation and these include exercise-induced reductions in body fat, especially visceral fat, increased production and secretion of anti-inflammatory cytokines from contracting muscle, downregulation of TLRs on monocytes and macrophages, and adaptations in intracellular generation of ROS.[33]

Much of the work focusing on the mechanisms, whereby exercise reduces inflammation has implicated adipose tissue. The current thinking is that physical inactivity and elevated caloric intake result in adipose tissue and adipocyte hypertrophy. As adipocytes grow beyond a critical size, the distance for oxygen diffusion becomes too great and the cells undergo hypoxic stress leading to necrosis or cell death. Necrosis is a potent stimulus for inflammatory responses as the innate immune system attempts to clean up the cellular debris and initiate adaptive and reparative response in the

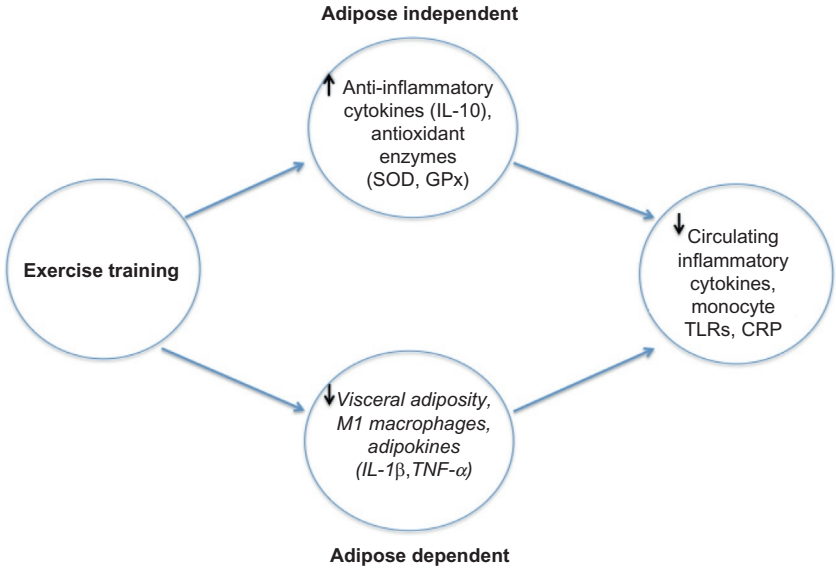

Figure 2 The effects of long-term, moderate intensity exercise training on inflammatory markers and immune mediators. The anti-inflammatory effects may manifest from both adipose-dependent and -independent mechanism. *Abbreviations*: IL, interleukin; SOD, superoxide dismutase; GPx, glutathione peroxidase.

inflamed adipose.[76] This effect is particularly damaging in visceral adipose tissue which seems to have a high inflammatory potential relative to subcutaneous fat. Exercise, by creating a caloric imbalance and mobilizing fat from adipose for fuel, reduces the size of the adipocytes thereby reducing hypoxic stress and inflammation. Indeed, we have found that 6 or 12 weeks of treadmill exercise training can significantly reduce both systemic and adipose tissue inflammation in mice fed a high-fat diet, suggesting that exercise-induced anti-inflammatory actions in adipose tissue are responsible for the reduced systemic inflammation in this model.[77]

Exercise and physical activity can also invoke anti-inflammatory actions independent of changes in fat mass. It has been suggested that, in the context of exercise, transient elevations in IL-6 coming from exercising skeletal muscle actually act in an anti-inflammatory fashion by inducing anti-inflammatory cytokines such as IL-1 receptor antagonist (IL-1RA) and soluble IL-10 which act to antagonize the actions of the quintessential proinflammatory cytokines IL-1β and TNF-α.[31] IL-6 also stimulates the release of cortisol which is an anti-inflammatory hormone.[35] Thus, IL-6 seems to be an important molecule that is elevated in response to

inflammatory stimuli and contributes to regulation of inflammatory reactions, but its measurement is frequently used as a biomarker for inflammation. There is also one study showing that aerobic exercise training decreases mononuclear cell production of TNF-α and IL-1α (atherogenic cytokines) and increases IL-4, IL-10, and TGF-β1 (atheroprotective cytokines) in individuals with high risks of heart disease.[78]

TLRs are highly evolutionarily conserved transmembrane proteins that play an important role in the detection of microbial molecular patterns and endogenous "danger signals," such as those induced by tissue damage.[79] Activation of TLRs results in the production of proinflammatory cytokines. Acute exercise can result in a reduction in the expression of TLR on blood monocytes[50] which would desensitize these cells to inflammatory stimuli thus contributing an anti-inflammatory effect. However, in animal experiments performed in our lab, exercise training failed to reduce the behavioral and inflammatory effects of a wide range of doses of LPS; a TLR4 ligand comprised of cell wall components of Gram-negative bacteria.[80]

The anti-inflammatory effect of exercise training may also be the result of modulation of intracellular signaling pathways mediated by nitric oxide (NO) and ROS. During exercise, increased production levels of NO and ROS are important in inducing anti-inflammatory defense mechanisms[81] and have long-term effects on muscle gene expression. Gielen *et al.* have reported that after exercise training, there is a significant reduction of NO synthase expression in skeletal muscle.[82] The adaptive responses of redox pathways in response to exercise training protect skeletal muscle from exposure to the increase of ROS following exercise.[81] In addition, TNF-α levels in skeletal muscle will be changed by ROS, which may reduce inflammation. Therefore, exercise-induced adaptation in redox-sensitive pathways may also attenuate inflammation.

8. SUMMARY

Exercise exerts a pleiotropic, time-dependent cascade of inflammatory events, which have numerous roles in health and disease. These include interactions between innate and adaptive immune cells, cytokines, and other intracellular components, which under appropriate conditions, provide an inflammatory milieu optimal for recovery, regeneration, and adaptation from an exercise bout. The inflammatory response to an acute exercise bout, however, does not necessarily provoke one type of "inflammatory environment," as the mode intensity and duration of exercise are vital

components of the exercise-induced inflammatory response. Nevertheless, it is evident that exercise training, over time, exerts anti-inflammatory actions through several distinct mechanisms. These include actions dependent and independent of changes in adipose tissue mass. Despite the mounting evidence regarding the anti-inflammatory potential of exercise, a mechanistic understanding into the key mediators and processes behind such response is still to be determined. As such, future research should encompass multicomponent approaches to exercise immunology, which attempt to integrate other, less-recognized physiological processes with acute and long-term inflammatory changes. This will include investigation into the metabolic, endocrine, and immune components of various tissues and organs, including the brain and GI. Ultimately, a more comprehensive understanding into the regulation of inflammation during and after exercise may be established.

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