


# Effect of Alpha-1 Antitrypsin and Irisin on Post-Exercise Inflammatory Response: A Narrative Review

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## Abstract

Physical activity has a positive effect on human health and emotional well-being. However, in both amateur and professional athletes, training poses a risk of acute or chronic injury through repetitive overloading of bones, joints, and muscles. Inflammation can be an adverse effect of intense exercise caused by several factors including oxidative stress. The present narrative review summarizes current knowledge on inflammatory markers induced by physical exercise. Post-exercise recovery may reduce inflammatory responses and is key to effective training and adaptation of muscle tissues to sustained physical exertion.

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## What's Known

- Activation of inflammatory response is essential for muscle repair and adaptation to exercise. However, excessive or persistent inflammation can lead to further tissue damage due to the nonspecific phagocytic function of inflammatory cells.
- Reducing inflammation has a beneficial effect on the recovery of muscle function after intense exercise.

## What's New

- Alpha-1 antitrypsin is a serine protease inhibitor involved in inflammatory responses.
- Blood biomarkers provide exact and reliable data to assess muscle damage and exercise-induced inflammation. These markers offer valuable insight into the relative state of recovery. Post-exercise recovery is key to effective training and adaptation to sustained physical exertion.

## Introduction

In recent years, there has been a growing awareness of the need for a healthy lifestyle, especially regular exercise. It is known that physical activity has a positive effect on overall health and can reduce the risk of severe health problems such as obesity and cardiovascular diseases.<sup>1, 2</sup> However, a vigorous workout is often associated with the development of microdamage in muscle tissue, which can lead to muscle soreness.<sup>3</sup> Functional recovery of muscles after tissue microdamage may take up to several days.<sup>4</sup> As a post-exercise response, intense physical activity may induce inflammation.<sup>2</sup> Therefore, the main challenge in sports medicine is to develop more effective methods to regenerate muscle tissue and accelerate the post-exercise recovery process. In particular, the type of recovery, and its ability to reduce the inflammatory response seems to be crucial for effective training and adaptation of muscle tissue to sustained physical exertion. The present narrative review summarizes current knowledge on exercise-induced inflammatory markers, and the effect of alpha-1 antitrypsin (AAT) and irisin on post-exercise inflammatory response. We also discuss the role of oxidative stress in triggering inflammation after physical activity. The findings of this study will help sports medicine professionals develop appropriate countermeasures against the adverse health effects of intense exercise.

### Course of the Inflammatory Process

Inflammation is a defense system in response to disrupted

homeostasis.<sup>5,6</sup> Tissue damage is known to trigger signals that activate the host's immune system against infectious agents to promote tissue repair.<sup>7</sup> Inflammatory response affects tissue homeostasis, increases blood flow, facilitates immune cell activation and migration, and triggers secretion of cytokines, chemokines, and growth factors.<sup>8,9</sup> Acute inflammation ultimately leads to the elimination of infectious agents, of damaged tissues, clearance of inflammatory cells, and return to homeostasis.<sup>10</sup> Persistent acute inflammation may develop into chronic inflammation, which can cause permanent tissue damage.<sup>11</sup> The process of inflammation is initially targeted locally and then centrally by inflammatory mediators circulating in the blood.<sup>12</sup> Neutrophils are key mediators and the first immune cells to respond to inflammation. These cells regulate acute inflammatory response by rapid release of reactive oxygen species (ROS), i.e., oxidative burst.<sup>13</sup> Neutrophils migrate to the site of injury through the bloodstream as a result of vasodilation and can increase vascular permeability caused by basophils or mast cell degranulation, activation of the complement system, or release of prostaglandins and leukotrienes.<sup>13</sup> In the early stage of endothelial injury, leukocytes migrate to the injury site for endothelial adhesion to the tissue.<sup>14</sup> Activation of neutrophils results in the release of many chemicals capable of attacking pathogens and mediators to activate other cells such as monocytes. Activated monocytes, in turn, produce and secrete interleukins, particularly interleukin 6 (IL-6), and other cytokines.<sup>5</sup> These mediators cause a nonspecific inflammatory response by inducing the production of acute-phase proteins (APPs), primarily by the liver, such as C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen, ferritin, AAT, ceruloplasmin, components of the complement system, and coagulation factors.<sup>15</sup> APPs affect homeostasis and thus trigger defensive and adaptive processes that contribute to short-term healing. However, they can also lead to chronic inflammation and tissue damage.<sup>13</sup> Next to macrophages and neutrophils, mast cells are also activated during the inflammatory response. These cells release histamine, proteolytic enzymes, and chemokines that significantly contribute to the progression of inflammation.<sup>16</sup>

In summary, inflammation is the response of the immune system to harmful stimuli, such as cell damage. The inflammatory response is a defense mechanism essential to maintaining homeostasis in organisms by suppressing noxious stimuli and initiating the healing process. Cellular and molecular interactions minimize

injury during acute inflammatory responses. However, uncontrolled acute inflammation can become chronic and contribute to various inflammatory diseases.

#### *Inflammatory Markers*

Activation of neutrophils releases inflammatory mediators that regulate the inflammatory cascade.<sup>17</sup> Secretion of chemokines and cytokines plays a significant role in modulating the inflammatory response through their capacity for cell surface binding and cell activation.<sup>16</sup> Cytokines are small secreted proteins synthesized by multiple cells in response to various stimuli.<sup>18</sup> They can be classified as pro-inflammatory, anti-inflammatory, and multifunctional cytokines.<sup>16,19</sup> They are pleiotropic because they affect different types of cells, and their effect depends on the type of cell they target.<sup>20</sup> Cytokines bind to specific receptors on cells with different origins and functions. In addition, they mediate signal transduction via various intracellular messengers and transcription factors.<sup>18</sup> Table 1 presents a list of cytokines and myokines that play a key role in the development of inflammatory processes.

The short half-life of cytokines suggests that these soluble mediators are rapidly eliminated under certain physiological conditions, thus ensuring their limited bioactivity.<sup>13</sup> Moreover, cytokines can modulate the response of an organism to stimuli by activating the hypothalamic-pituitary-adrenal axis.<sup>26</sup> The final stage of acute inflammatory response is dominated by mediators involved in suppressing inflammation,<sup>27</sup> during which they control the spread of inflammation, limit inflammatory responses, and facilitate the final stage of muscle repair.<sup>16</sup>

#### *Characteristics of Cytokine Response to Exercise*

IL-6 is a multifunctional cytokine that plays an important role in activating host defense mechanisms by regulating the immune response, mediating acute phase response, and hematopoiesis.<sup>28,29</sup> It promotes B-cell differentiation,<sup>29</sup> an important inducer of APPs in liver cells, and is involved in the proliferation and differentiation of T cells.<sup>28,30</sup> Therefore, it might be a valuable marker of stress and muscle recovery.<sup>31</sup> IL-6 also increases adipose tissue lipolysis, improves insulin sensitivity,<sup>32</sup> and induces an increase in the production of anti-inflammatory cytokines such as IL-10.<sup>33</sup> IL-6 is an important marker of inflammation, because an increase in its concentration is associated with an increase in APPs concentration.<sup>34</sup>

**Table 1:** Cytokines and myokines that play a key role in the development of inflammatory response

Cytokine/Myokine	Origin	Function	Article
Interleukin 1 (IL-1)	Macrophages, dendritic cells, T and B lymphocytes	Activation of T and B lymphocytes, enhancing the production of other cytokines and acute phase proteins, induction of adhesive molecules	Germolec et al. <sup>13</sup>
Interleukin 6 (IL-6)	Macrophages, dendritic cells, B cells, activated T cells	Development of myeloid cells, regulation of acute phase proteins	Germolec et al. <sup>13</sup>
Interleukin 8 (IL 8)	Monocytes, macrophages	Recruitment and activation of immunocompetent cells, stimulation of chemotaxis, and angiogenesis	Remick <sup>21</sup>
Interleukin 10 (IL-10)	Macrophages, dendritic cells, regulatory B and T lymphocytes	Inhibition of pro-inflammatory cytokines	Germolec et al. <sup>13</sup>
Transforming growth factor beta (TGF-β)	Macrophages, megakaryocytes, chondrocytes	Inhibition of cytokine production and activity, inhibition of B-cell proliferation, stimulation of wound healing	Germolec et al. <sup>13</sup>
Tumor necrosis factor alpha (TNF-α)	Macrophages, dendritic cells, lymphocytes, mast cells	Increase in MHC expression, macrophage activation, enhancing the destruction of cancer cells	Germolec et al. <sup>13</sup>
Irisin	Muscle cells	Inhibition of pro-inflammatory cytokines	Lin et al. <sup>22</sup>
Decorin	Muscle cells, fibroblasts, endothelial cells	Cell-matrix crosstalk modulation, promotion of hypertrophy of muscle fibers	Sabouri et al. <sup>23</sup>
Apelin	Adipocytes, monocytes	Regulation of energy homeostasis	Ramezani et al. <sup>24</sup>
Musclin	Muscle cells	Regulation of energy homeostasis	Clark et al. <sup>25</sup>

Tumor necrosis factor alpha (TNF-α) is a polypeptide cytokine produced by monocytes and macrophages that acts as a multipotent modulator of the immune response.<sup>35</sup> TNF-α in the circulation activates neutrophils, changes the properties of vascular endothelial cells, and regulates the metabolic activity of tissue in response to infection or tissue damage.<sup>35</sup> Transforming growth factor beta (TGF-β) is another pleiotropic cytokine with strong immunoregulatory properties. TGF-β family includes six isoforms, but only TGF-β1, TGF-β2, and TGF-β3 have been identified and expressed in mammals. TGF-β regulates fundamental aspects of cellular function, such as growth, differentiation, adhesion, migration, apoptosis, extracellular matrix production, and inflammation.<sup>36</sup>

Interleukin 8 (IL-8) is a pro-inflammatory chemokine secreted by monocytes, macrophages, and endothelial cells that activates neutrophils.<sup>37</sup> It plays an important role in regulating the acute inflammatory response. It is quickly synthesized at the site of inflammation, where it recruits and activates immunocompetent cells.<sup>23</sup> IL-8 is not only released early in the inflammatory response, but its levels remain increased for several days or weeks.<sup>23</sup> Another pro-inflammatory cytokine is interleukin-1 beta (IL-1β), a member of the interleukin-1 family, which can stimulate T and B lymphocytes, increase cell proliferation, and initiate or suppress gene expression of several proteins.<sup>38</sup> Whereas interleukin 10 (IL-10) is an anti-inflammatory cytokine that plays a vital

role in regulating the functions of lymphoid and myeloid cells. It also regulates the proliferation and differentiation of B cells, mast cells, and thymocytes.<sup>39</sup>

#### *Characteristics of Lysosomal Enzyme Response to Exercise*

Lysosomes are organelles involved in the intracellular digestion of various macromolecules that have entered the cell through endocytosis, and those derived from the cell's cytoplasm.<sup>40</sup> They are also involved in the apoptosis process.<sup>41</sup> Lysosomal enzymes include about 40 acid hydrolases, namely lipases and phospholipases, nucleases, phosphatases (e.g., acid phosphatase), sulfatases (e.g., arylsulfatase A), proteases (e.g., cathepsin D), and other glycosidases.<sup>42</sup>

Acid phosphatase (ACP) is a lysosomal enzyme associated with cells' physiological and pathological functions<sup>43</sup> and is present in different cells and tissues. In particular, epithelial cells of the prostate gland are characterized by high ACP activity.<sup>44</sup> It catalyzes the hydrolysis of phosphate monoesters in acidic conditions (pH 4-7).<sup>45</sup> In addition, it is an enzyme involved in the degradation of phagocytosed materials found in neutrophils and monocytes.<sup>46</sup> ACP also plays a role in the biological activation of lymphocytes, their blastic transformation, and the removal of cell organelles during mitosis.<sup>47</sup>

Arylsulfatase A (ASA) belongs to the group of sulfatases that plays a role in many physiological processes.<sup>48</sup> Arylsulfatases can be expressed in tissues of various organs (e.g., liver, skin, lymph

nodes) and nervous tissue.<sup>48</sup> They can also be detected in urine and blood serum.<sup>49</sup> However, the highest activity of ASA is found inside lysosomes.<sup>49</sup> Human arylsulfatase catalyzes reactions at both acidic and neutral pH.<sup>50</sup> ASA catalyzes the degradation of sulfatides to galactosylceramides (GalC), starting with the hydrolysis of the sulfate residue.<sup>48</sup> Cathepsin D (CTSD) is a soluble lysosomal aspartic endopeptidase synthesized in the rough endoplasmic reticulum as procathepsin D.<sup>51</sup> After removal of signal peptide, procathepsin D is directed to intracellular vesicular structures (lysosomes, endosomes, and phagosomes). In the cell, CTSD is localized in lysosomes and binds to the membranes of erythrocytes and macrophage endosome vesicles.<sup>52</sup> The primary function of enzymatically active CTSD is the degradation of proteins in the acidic environment of lysosomes. Active forms of CTSD and other proteases can be released from lysosomes into the cytoplasm in response to apoptotic stimuli, thus contributing to cell death.<sup>51, 52</sup> In addition, it participates in blood clotting and fibrinolysis.<sup>51</sup> CTSD activates other proteases, such as cathepsin B, cathepsin L, collagenases, caspases-3, and caspases-9.<sup>53</sup> The proteolytic activity of CTSD is modulated by several physical and chemical factors, including pH, metabolic products, growth factors, exogenous and endogenous inhibitors, and hormones.<sup>54</sup>

#### *Characteristics of Alpha-1 Antitrypsin (AAT)*

AAT is a protein belonging to the family of serine protease inhibitors, called serpins.<sup>55</sup> It is produced in various tissues and cells, including monocytes, pulmonary macrophages, and phagocytes; but primarily by hepatocytes.<sup>56</sup> AAT is an APP with anti-inflammatory properties.<sup>57</sup> Its main biochemical activity is the regulation of neutrophil elastase.<sup>56</sup> In addition, AAT reduces the production of pro-inflammatory cytokines, inhibits apoptosis, blocks leukocyte degranulation and migration, and modulates local and systemic inflammatory responses.<sup>58</sup> Inhibitory properties of this glycoprotein against serine proteases maintain the protease/antiprotease balance in the body, which is the primary mechanism protecting against uncontrolled proteolysis in tissues.<sup>59</sup> AAT is responsible for approximately 80-90% of antiprotease activity in blood plasma.<sup>60</sup> One of the essential functions of this protein is to inhibit the activity of neutrophil elastase and trypsin by forming inactive complexes with them. It also inhibits cathepsin released from neutrophils and blocks the cytotoxicity of neutrophils and their effect on IL-8 produced by epithelial cells.<sup>57</sup>

Moreover, the presence of methionine groups in the active center of this glycoprotein indicates its possible antioxidant activity.<sup>61, 62</sup>

#### *Post-exercise Inflammation*

Regular exercise generally strengthens muscles and increases their resistance to fatigue.<sup>63</sup> However, during intense exercise, tired muscles are temporarily weakened.<sup>64</sup> In untrained individuals, a single series of moderate to vigorous exercise can damage muscles and activate neutrophils in response to developing inflammation, ultimately causing muscle soreness.<sup>65</sup> It was shown that exercise produces a response similar to the acute phase in response to sepsis or mechanical tissue trauma.<sup>66</sup> Activation of inflammatory response is essential for muscle repair and adaptation to exercise. On the other hand, excessive or persistent inflammation is believed to contribute to further tissue damage due to nonspecific phagocytic function of inflammatory cells, such as neutrophils.<sup>67</sup> Therefore, reducing inflammation may have a beneficial effect on the recovery of muscle function after intense exercise.<sup>68</sup> Both endurance exercise and interval training induce metabolic stress in active skeletal muscles associated with a high rate of aerobic respiration and heat production.<sup>69</sup> After training, there is often an increase in markers of skeletal muscle damage in the blood, such as creatine kinase (CK) or lactate dehydrogenase (LDH).<sup>70, 71</sup> CK is a frequently used diagnostic marker for detecting exercise-induced muscle damage.<sup>72</sup> Moreover, increased serum CK activity after exercise is inversely proportional to muscular strength.<sup>73, 74</sup> LDH is an enzyme that catalyzes the final step of anaerobic glycolysis, regenerating nicotinamide adenine dinucleotide reduced (NADH) to oxidized (NAD<sup>+</sup>) form by converting pyruvate to lactate.<sup>75</sup> This enzyme is involved in the metabolism of muscles, and its activity is constantly present in the blood serum as a result of energy expenditure. However, LDH activity increases significantly after intensive physical exercise.<sup>76</sup> Serum LDH indicates the degree of metabolic adaptation of skeletal muscles to physical training.<sup>77</sup> In addition, after exercise, an increase in the concentration of inflammatory markers (e.g., selected interleukins, CRP, etc.) may be observed.<sup>2, 78</sup> A previous study reported increased concentrations of markers (CRP, myoglobin, CK) associated with inflammation and muscle injury in the blood sample of athletes after two ultra-endurance mountain races of different distances (54 and 111 km).<sup>74</sup> Regular training was shown to lower CRP levels compared to baseline.<sup>79</sup> This is due to

various mechanisms and processes during the adaptation of an organism to workload. A high concentration of CRP after exercise indicates a lack of adaptation to physical exertion or overtraining, primarily due to oxidative stress and inflammation.<sup>32</sup>

Oxidative stress is also important in modulating the inflammatory response after exercise. However, the association between inflammatory mediators (e.g., cytokines) and oxidative stress is not fully explained. Increasing demand for energy after exercise causes greater oxygen consumption by mitochondria and thus increases ROS production.<sup>80</sup> Superoxide ( $O_2^-$ ) and nitrogen monoxide (NO) are the main free radicals that trigger a chain reaction of hydrogen peroxide ( $H_2O_2$ ), hydroxyl radicals ( $OH^-$ ), peroxynitrite ( $ONOO^-$ ), and hypochlorous acid (HOCl). All these free radicals can cause immune reactions and cellular signaling. However, they also have negative effects, such as causing oxidative damage to lipids or proteins.<sup>81</sup> ROS is produced by a leak of single electrons in the respiratory chain in the inner membrane of mitochondria of the contracting muscle cells.<sup>82</sup> Other sources of ROS in muscle fibers during physical exercises can increase the activity of phospholipase A2 (PLA2), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and xanthine oxidase (XO).<sup>83</sup> NADPH oxidase is believed to increase the production of superoxides by releasing electrons, whereas XO produces superoxides by converting hypoxanthine into xanthine and uric acid.<sup>81</sup> The main source of ROS during physical activity probably depends on the type of exercise.<sup>84</sup> Intensive exercise can trigger muscle injuries, which activate neutrophils and macrophages via interferon- $\gamma$  (IFN- $\gamma$ ), IL-1, and TNF. These immune cells excessively produce ROS by oxidative burst, a main component of the neutrophil defense mechanism.<sup>82</sup> NO production increases during exercise to improve vascularization and skeletal muscle function by modulating microcirculation. Consequently, superoxide anions react with NO to produce different forms of reactive nitrogen (RNS), causing further ROS generation and reducing NO bioavailability.<sup>85</sup> When redox homeostasis is disrupted, cells become vulnerable to ROS attack, resulting in oxidative damage to cellular components.<sup>86</sup> High levels of ROS lead to peroxidation of cell membranes and damage to numerous macromolecules, including DNA.<sup>87</sup> In addition, ROS destabilizes muscle cell structures, including the sarcolemma. Prolonged high-energy transformation to sustain repetitive contractions and increased intramuscular

pressure induces mild hypoxic stress on the muscle fibers, resulting in the accumulation of metabolites, which in turn increase the osmolality of cells.<sup>69</sup> Damage to the cell membrane of myocytes increases permeability to various substances.<sup>69</sup> When skeletal muscles are damaged, sarcolemma is destabilized, and extracellular calcium ions immediately enter the damaged cells. Subsequently, myocyte degeneration begins by activated calpain, a calcium-dependent neutral protease protein.<sup>88</sup> Structural changes in muscle fibers are also accompanied by increased release of some intracellular enzymes.<sup>89, 90</sup> Lysosomal membranes may be damaged after exercise, resulting in lysosomal enzymes entering the cytoplasm. Subsequently, they are released from cells into the bloodstream and can contribute to inflammation.<sup>91-93</sup> In the acute phase, polymorphonuclear leukocytes are the most abundant cells at the injury site. However, they are replaced by monocytes during the first day of the inflammatory reaction. Based on the basic principles of inflammation, these monocytes are eventually converted into macrophages and then actively engaged in the proteolysis and phagocytosis of necrotic material by releasing lysosomal enzymes.<sup>94</sup> The main function of the acute phase response is to protect tissues from further injury and return to homeostasis.<sup>95</sup> Immune stress induces the production of pro-inflammatory cytokines that diffuse into the circulation, which in turn causes the liver to promote the secretion of APPs such as CRP, serum amyloid P (SAP), SAA, or AAT.<sup>15</sup> Serine protease inhibitors are proteins that regulate and control crucial physiological processes, such as inflammation, coagulation, thrombosis and thrombolysis, and immune responses.<sup>96</sup> AAT inhibits the protease elastase produced by neutrophils during an inflammatory response. It is possible that increased AAT indirectly inhibits complement activation.<sup>97</sup> It was shown that AAT reduces the production of pro-inflammatory cytokines, inhibits apoptosis and inflammatory reactions.<sup>58</sup> Several studies reported that AAT activity is increased post-exercise.<sup>98-101</sup> Another study reported post-exercise increase of both IL-6 concentration and AAT activity, which may confirm that the release of pro-inflammatory cytokines stimulates the release of APPs.<sup>93</sup>

Muscle activity increases ROS production and enhances the body's antioxidant defense system. Antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX) are the primary defense against ROS generated during exercise, as their levels increase in response

to exercise.<sup>82</sup> Some studies that evaluated the effect of exercise have shown increased ROS production and antioxidant activity of enzymes.<sup>86, 102, 103</sup> Ammar and colleagues reported increased SOD and GPX activity in healthy, untrained men after exercise.<sup>83</sup> Increased antioxidant activity may result from adaptation to increased ROS concentrations.<sup>104</sup> Therefore, regular exercise may improve antioxidant ability and maintain oxidant-antioxidant balance.<sup>84</sup> Habitual intense training is shown to reduce lipid peroxidation products and prevent oxidative damage in tissues.<sup>105</sup> Low concentrations of ROS are essential for proper regulation of cellular function and adaptation to exercise-induced stress. Well-trained athletes were shown to be more susceptible to oxidative stress.<sup>106</sup> As a result of muscle tissue damage caused by ROS, inflammatory mediators involved in initiating the inflammatory response are released at the site of damage.<sup>69, 107</sup> Exercise can trigger acute phase response characterized by an increase in peripheral blood levels of cytokines and chemokines.<sup>80</sup>

The immune system plays a significant role in the degeneration and regeneration of muscles and surrounding connective tissue after exercise-induced damage.<sup>108</sup> Cytokines play a particular role in maintaining the balance between beneficial and adverse physiological effects of the immune system response to exercise.<sup>109</sup> IL-6 has both pro- and anti-inflammatory properties,<sup>31</sup> and may modulate anti-inflammatory response.<sup>32</sup> It was shown that after intense physical exercise, the levels of TNF- $\alpha$  and IL-1 $\beta$  increase by a factor of two, and IL-6 may increase up to 100-fold.<sup>79</sup> Moreover, concentrations of chemokines, IL-8, and macrophage inflammatory proteins (MIP-1 $\alpha$  and MIP-1 $\beta$ ) are elevated after intense exercise.<sup>79</sup> TNF- $\alpha$  appears to be the first systemically released cytokine, with concentrations peaking within hours after inflammatory response. Shortly after, IL-1 concentration increases followed by an increase in IL-6. Anti-inflammatory cytokines are released in response to increasing levels of pro-inflammatory cytokines to inhibit and prevent tissue damage.<sup>14, 110</sup> Increased levels of IL-6, IL-10, IL-8, and inflammatory cytokines after exercise were reported.<sup>78, 111</sup> On the other hand, another study reported increased plasma IL-1 $\beta$  levels after acute high-intensity street dance exercise.<sup>107</sup> It was also shown that changes in TGF- $\beta$  concentration can be involved in the process of human body adaptation to exercise.<sup>36</sup> Over the past decade, researchers have highlighted the biological effect of muscle-derived cytokines (i.e., myokines) in regulating cellular metabolism in skeletal muscle and adipose tissue. A small number of studies have examined the relationship

between released cytokines and markers of muscle damage to establish whether cytokines are the cause or by-product of exercise-induced muscle damage.<sup>64</sup>

Several types of immune cells (e.g., mast cells, neutrophils, T-regulatory cells, eosinophils, CD8 T cells) were shown to infiltrate damaged skeletal muscles.<sup>112</sup> Leukocytes build up in the muscles immediately after exercise and accumulate in the extracellular space in the muscle tissue 24-48 hours after exercise.<sup>112</sup> Macrophages, the predominant leukocyte type, are observed at each time point of skeletal muscle regeneration after injury and perform specific functions throughout the process.<sup>113</sup> Macrophages invading damaged muscle tissue produce several growth factors that stimulate and promote muscle regeneration *in vitro*. Some growth factors, such as insulin-like growth factor 1 (IGF-1) and TGF- $\beta$ 1 are known to regulate the activation of satellite cells.<sup>88</sup> These cells are activated in response to adequate stimulus, which initiates proliferation.<sup>114</sup> Subsequently, they migrate to areas where they differentiate and fuse with existing muscle fibers or form new fibers.<sup>88</sup> It was found that exercise can stimulate satellite cells to re-enter the cell cycle and multiply.<sup>64</sup> After the removal of necrotic tissue, satellite cells regenerate skeletal muscle tissue by regulating transcription factors.<sup>106</sup>

#### *Characteristics of Irisin*

Skeletal muscle secretes numerous myokines, which are synthesized and secreted by myocytes in response to muscle contraction. Myokines exert an autocrine function in regulating muscle metabolism.<sup>115</sup> Irisin is a novel myokine released after exercise.<sup>116</sup> It is a peptide derived from proteolytic cleavage of fibronectin type III domain-containing protein 5 (FNDC5). FNDC5 is a type I transmembrane protein predominantly present in skeletal muscles.<sup>117, 118</sup> Some studies suggested that irisin may be involved in the regulation of energy metabolism.<sup>115, 116</sup> Rashid and others reported that this myokine improves glucose homeostasis after long-term moderate physical exercise.<sup>117</sup> Several studies have suggested that irisin is directly associated with the beneficial effects of regular exercise. It is shown that exercise increases serum concentration of irisin.<sup>119, 120</sup> By entering the bloodstream, irisin circulates to organs and tissues and acts as a strong inhibitor of pro-inflammatory cytokines.<sup>121</sup> Irisin is therefore a factor that explains numerous metabolic adaptations induced by exercise. However, further studies are required to elucidate the role of irisin in regulating the production of pro-inflammatory cytokines during exercise. It

was reported that irisin modulates mitochondrial fusion, fission, and biogenesis to suppress oxidative stress.<sup>122</sup> Irisin concentration at rest is positively correlated with malondialdehyde, a biomarker of oxidative stress. However, it is negatively correlated with the antioxidant protection marker, *i.e.*, the capacity to absorb oxygen radicals in response to exercise.<sup>122</sup> This, in turn, clarifies the association between irisin and oxidative stress in athletes with overtraining syndrome.

### Practical Implications

Skeletal muscle regeneration is a highly synchronized process involving the activation of several cellular and molecular responses.<sup>123</sup> It involves interactions between inflammatory cells, fibroblasts, and endothelial cells, as well as their secreted soluble factors.<sup>124</sup> In recent years, sports medicine professionals have faced new challenges as a result of sports development initiatives. Proper training programs should balance the systemic stressors experienced by athletes with personalized plans to improve performance and reduce exercise-induced stress symptoms. The use of blood biomarkers, including new myokines secreted from skeletal muscle, provides a faster and potentially more accurate method for assessing muscle damage and exercise-induced inflammation. In addition, they offer valuable insight into the relative state of recovery. However, despite their high accuracy, there is a lack of consensus about the time course and magnitude of their appearance and clearance from the blood following different types or intensities of exercise.<sup>125</sup> To date, there is no explicit data on the ability of organisms to regenerate and reduce inflammation. Moreover, there is no published scientific evidence to aid the selection of the most appropriate post-exercise recovery method between training sessions. Therefore, an in-depth understanding of inflammatory response due to exercise is essential.

### Conclusion

The accumulation of cytokines, neutrophils, and macrophages is directly associated with muscle tissue damage. Understanding the inflammatory response and mechanism of exercise-induced myokines allows the identification of inflammatory markers involved in muscle damage and regeneration. The type of post-exercise recovery that may reduce inflammatory responses seems to be key to effective training and adaptation of muscle tissues to long-term physical exertion. Further studies are required to elucidate the exact underlying mechanisms

of these beneficial effects. Based on our current knowledge, such an approach would reduce post-exercise muscle damage, which can protect the health and physical integrity of athletes and increase their chances of achieving training goals.

### Authors' Contribution

C.M-K: Research conception and supervision. M.P, C.M-K: Drafting and revising the manuscript. Both authors have approved the final version of the manuscript for publication

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