

# The Dual Role of Myokines in Fatigue Associated with Inflammatory Joint Diseases

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**Abstract:** Fatigue is a prevalent and debilitating symptom in rheumatic diseases such as rheumatoid arthritis and psoriatic arthritis. Despite advances in reducing inflammation through treatments, fatigue often persists, underscoring its multifactorial etiology. A possible link between the persistent inflammation observed in rheumatic diseases and the onset of fatigue has been suggested. The discovery that skeletal muscles also secrete cytokines and myokines, has opened new avenues for research. This narrative review explores current mechanistic insights and evidence on the dual role of myokines in exacerbating or alleviating fatigue, particularly in the context of physical activity and chronic inflammation. Key myokines such as interleukin-6 (IL-6), myostatin, interleukin-15 (IL-15), brain-derived neurotrophic factor (BDNF), and irisin are examined for their influence on muscle-brain communication, neuroinflammation, and systemic metabolic processes. The findings highlight the potential of targeted myokine modulation as a therapeutic strategy for fatigue management.

**Keywords:** myokines, fatigue, rheumatoid arthritis, physical exercise

## Introduction

Fatigue is a common and debilitating symptom in rheumatic diseases like rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. It is characterized by persistent tiredness and exhaustion, significantly impacting patients' life quality and worsening their disability. The causes of fatigue in these diseases are complex and multifaceted, involving physiological, psychological, and social factors. For patients with rheumatic disease fatigue significantly impacts the life quality and ability to perform daily activities. Chronic inflammation, a hallmark of rheumatic diseases, is believed to play a significant role in fatigue development.<sup>1</sup> In patients with rheumatoid arthritis the relationship between disease activity (as measured for example, by the Disease Activity Score-28 - DAS-28 scale) and fatigue is inconsistent and varies between studies.<sup>2–5</sup> Fatigue shows a strong association with pain, mood disorders, sleep disturbances, obesity, and comorbidities.<sup>4</sup> The association between fatigue and disease activity in rheumatoid arthritis (RA) is complex and not fully understood. While some studies have shown a correlation with disease activity measures like DAS-28, other studies have reported no correlation.<sup>6–8</sup> The etiology of fatigue in inflammatory joint diseases is multifactorial, with both disease-related and patient-specific factors contributing to its development. The main symptoms of joint disease, including pain, stiffness, and swelling, can contribute to the fatigue experience.<sup>9</sup> Additionally, the systemic inflammatory response associated with exhaustion can lead to the release of cytokines and other inflammatory mediators, which have been linked to the development of fatigue.<sup>10</sup> Cytokines guide immune cell migration and shape the immune response. The type of cytokines released during immune activation influences whether the response is cytotoxic, humoral, cell-mediated, or allergic. Inflammatory stimuli trigger a cascade of cytokine interactions, often requiring multiple cytokines to act synergistically. Importantly, a cytokine's function can vary depending on the context—its cellular source, target cells, and the immune phase.<sup>11</sup> Among the key mediators involved in this process are pro-inflammatory cytokines such as

interleukin-1 beta (IL-1 $\beta$ ), interleukin-6, and tumor necrosis factor alpha (TNF- $\alpha$ ), which affect both the central nervous system and peripheral tissues, thereby promoting fatigue-related symptoms. IL-6, in particular, is recognized as a dual-function cytokine that not only mediates acute-phase inflammatory responses but also contributes to the development of sickness behavior and fatigue through its central effects on the hypothalamic–pituitary–adrenal axis.<sup>12</sup>

Myokines are small proteins produced by muscle cells, and they have been shown to play a role in regulating inflammation.<sup>13</sup> The production and secretion of myokines by skeletal muscle is tightly regulated by various physiological and pathological stimuli. These regulatory mechanisms reflect the dynamic interplay between muscle activity, metabolic state, and systemic inflammation. Myokines are not constitutively expressed at high levels; instead, their release is often stimulated by acute or chronic changes in muscle function and suppressed by adverse metabolic or inflammatory conditions.<sup>14</sup> Muscle contraction induces the expression of several key myokines, including interleukin-6, interleukin-15, irisin, and brain-derived neurotrophic factor. During exercise, metabolic stress activates intracellular pathways such as adenosine monophosphate-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 $\alpha$ ), promoting the release of irisin and BDNF, which play important roles in inflammation regulation and energy metabolism.<sup>15</sup> Other factors stimulating myokine production include: oxidative stress and hypoxia, pro-inflammatory cytokines like TNF- $\alpha$  and IL-1 $\beta$ , anabolic hormones (eg, testosterone, growth hormone), which support IL-15 expression and muscle anabolism.<sup>16–18</sup> Conversely, a sedentary lifestyle is associated with decreased production of beneficial myokines and a shift toward a pro-inflammatory profile. Chronic diseases such as sarcopenia or cachexia often reduce levels of IL-15 and irisin while promoting catabolic factors like myostatin, a negative regulator of muscle mass and myokine secretion.<sup>19</sup> Other inhibitory factors include psychological stress and depression, which lower BDNF levels and disrupt hypothalamic–pituitary–adrenal axis function,<sup>20</sup> as well as obesity and metabolic syndrome, which alter myokine profiles and blunt their anti-inflammatory potential.<sup>21</sup>

While current therapies effectively reduce inflammation and disease activity in rheumatic conditions, fatigue often persists, highlighting the need for a more comprehensive understanding and management approach.<sup>22</sup> Unfortunately, fatigue is often underestimated clinically, because it is a subjective experience reported by the patient, unlike objective disease markers like pain, stiffness, swelling, and inflammatory markers. Perhaps exploring myokine modulation could offer a new avenue for managing fatigue in inflammatory joint diseases, even when traditional treatments successfully address inflammation. Therefore, effectively managing fatigue in inflammatory joint diseases requires a multifaceted approach that includes identifying and thoroughly assessing the individual patient's subjective experience of fatigue.

This review aims to summarize current knowledge on the regulatory functions of myokines in the context of fatigue associated with inflammatory joint diseases, with particular focus on their potential contribution to systemic inflammation, neuroimmune modulation, and therapeutic prospects beyond conventional anti-inflammatory treatments.

## Background on Myokines

The World Health Organization (WHO) defines physical activity as any movement produced by skeletal muscles that requires energy expenditure. It includes all forms of movement, such as leisure-time physical activity, travel to and from places, and occupational duties. Both moderate and vigorous physical activity have beneficial effects on health.<sup>23</sup> While the benefits of physical exertion are widely known, the mechanisms by which physical activity and muscle contraction contribute to them are still being elucidated, with myokines playing a pivotal role in these processes.<sup>24</sup>

Numerous studies have proven, that physical exercise has a beneficial effect on reducing the risk of lifestyle diseases such as cardiovascular diseases (CVD), type 2 diabetes mellitus (T2DM), and hypertension. Physical inactivity and a sedentary lifestyle are significant alterable risk factors for heart disease, overall mortality globally, type 2 diabetes mellitus, colon cancer, postmenopausal breast cancer and osteoporosis.<sup>25,26</sup> For many years, it was unclear how physical exercise beneficially influences many metabolic processes. Initially, it was hypothesized, that contracting muscles influence metabolic processes through the nervous system. This theory was disproven in studies with patients with spinal cord injuries, where stimulation of paralyzed muscles also contributed to changes in physiological processes.<sup>27</sup> Therefore, skeletal muscles that contract need to be capable of signaling to other organs through substances released into the bloodstream during exercise. These substances can have a direct or indirect impact on the functioning of other organs, including fat tissue, liver, heart, blood vessel system, and the brain.<sup>28</sup> The work of Henningsen et al has shown that

muscles should also be regarded as secretory organs that produce proteins, cytokines, and growth factors.<sup>29</sup> A significant contribution to the study of muscles as a secretory organ is owed to Pedersen et al, who not only introduced the term myokines to describe cytokines and small proteins produced by contracting skeletal muscles, but also described the functions of these molecules.<sup>26</sup> Myokines exert their effects on other tissues and organs through autocrine, paracrine, and endocrine pathways.<sup>30</sup> Receptors for myokines are found in various tissues, and among the target organs, like liver, central nervous system, pancreas, bones, skin, adipose tissue, and muscles.<sup>31</sup> Myokines play a role in the maintenance of energy balance, in the sugar and fat metabolism, and in the neovascularization.<sup>32</sup> They are also involved in metabolic changes induced by physical exertion, adaptation to training, tissue regeneration, immunomodulation, and cell signaling.<sup>33</sup> They are crucial elements in understanding the intricate regulatory mechanisms of the body, especially concerning physical activity and health. The endocrine functions attributed to myokines are associated with body weight regulation, mild inflammation, insulin sensitivity, inhibition of tumor growth, and improvement of cognitive function.<sup>34</sup> Most of the described myokines are not molecules produced solely by muscle cells but also by other tissues including macrophages and adipose tissue.<sup>35</sup> Myokines are distinct from adipokines, which are secreted primarily by adipose tissue and are often associated with the promotion of low-grade systemic inflammation and metabolic disorders. While both myokines and adipokines belong to the broader family of cytokines and influence immune and metabolic homeostasis, their tissue origin and predominant physiological functions are fundamentally different. This distinction is especially relevant in the context of chronic inflammatory and metabolic diseases, where imbalances in the secretion of both myokines and adipokines can contribute to disease progression.<sup>36</sup>

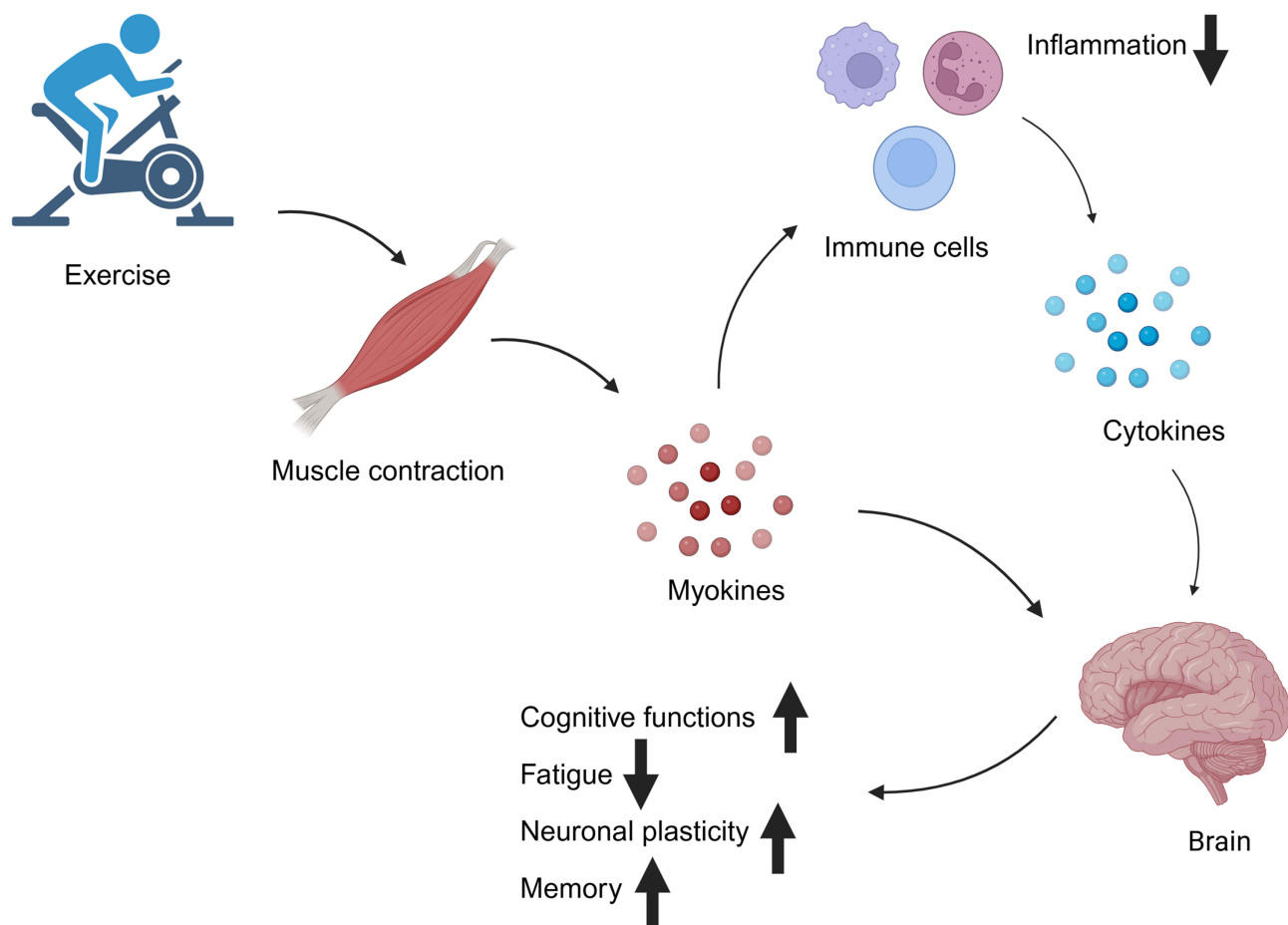
It is believed that skeletal muscles can produce and secrete different myokines. Muscle tissue in non-obese individuals can constitute approximately 40% of body mass, making it the largest secretory organ.<sup>37</sup> Different myokines play key roles in inflammation and muscle function. Several myokines play crucial roles in muscle growth, metabolism, and other physiological processes. IL-6, for example, exhibits both pro- and anti-inflammatory properties, influencing energy metabolism and muscle growth.<sup>38</sup> Other myokines like interleukin-15 also contribute to muscle growth and regulate adipose tissue, while myostatin acts as an inhibitor of muscle growth and differentiation.<sup>39,40</sup> Additionally, irisin promotes the browning of white adipose tissue and may support neuron growth.<sup>41</sup> Interestingly, skeletal muscle activity can influence brain health through the production of brain-derived neurotrophic factor. Contractions stimulate BDNF release, which then acts as a myokine, promoting fat oxidation via adenosine monophosphate (AMP)-activated protein kinase activation.<sup>42</sup>

Skeletal muscles, previously not considered significant in pathogen defense, are now recognized as active participants in immune responses.<sup>43</sup> They are not only targets for cytokines but also contribute to defense mechanisms.<sup>44</sup> Research from the 1970s highlighted the importance of regular muscle stimulation through exercise, which improves the body's defense against opportunistic infections.<sup>45</sup> This improvement is linked to glutamine, an amino acid primarily produced by active skeletal muscles. Glutamine serves as the main energy source for rapidly dividing immune cells like lymphocytes and macrophages and enhances phagocytosis, antigen presentation, cytokine production, and proliferation.<sup>43</sup> The innate immune response, like the peripheral nervous system, comprises afferent and efferent pathways and skeletal muscles are involved in both responses. Muscle cells have numerous pattern recognition receptors (PRRs) that detect components or products of invasive microorganisms (eg, lipopolysaccharide - LPS, foreign DNA/RNA) known as pathogen-associated molecular patterns (PAMPs).<sup>46,47</sup> Other PRRs recognize damage-associated molecular patterns (DAMPs).<sup>48</sup> Recently, metabolism-associated molecular patterns, activated by metabolites and excess nutrients, have also been identified (MAMPs).<sup>49</sup> Toll-like receptors are key PRRs in skeletal muscle, activated by various PAMPs, DAMPs, and MAMPs.<sup>50</sup> Nucleotide-binding oligomerization domain-like receptors (NOD-like receptors), specifically NOD1 and NOD2, are also important, recognizing bacterial peptidoglycans. Their activation triggers a pro-inflammatory pathway via nuclear factor kappa B, supporting the immune response.<sup>51</sup>

Besides pathogen-recognizing receptors, skeletal muscles also have receptors for inflammatory cytokines (eg, TNF- $\alpha$ , IL-1 $\beta$ , IL-6). Activating these receptors triggers metabolic changes and immune responses, aiding defense against infections.<sup>52</sup> These cytokines reach muscles via the bloodstream from other organs, but skeletal muscles also synthesize them directly and therefore they are known as myokines.<sup>53</sup> Myokines regulate inflammation, metabolism, tissue regeneration, and exercise adaptation.<sup>54</sup> Myokines secreted by contracting muscles are key to the health benefits of

exercise.<sup>55</sup> Regular activity stimulates their production, helps regulate inflammation, improves metabolism, and supports tissue regeneration.<sup>34</sup> The impact of physical exercise and myokines on the central nervous system is presented in the **Figure 1**. Conversely, a sedentary lifestyle disrupts myokine production and function, leading to chronic inflammation, muscle loss (sarcopenia), fat accumulation, and increased risk of cardiovascular diseases, insulin resistance, and type 2 diabetes mellitus. Thus, regular exercise is crucial for preventing these conditions by supporting healthy myokine production.<sup>32</sup> Recent evidence suggests that myokines may also play a significant role in the pathophysiology of osteoarthritis, particularly through their influence on cartilage metabolism, subchondral bone remodeling, and local inflammation. For example, irisin, IL-6, and myostatin have been implicated in modulating chondrocyte function and cartilage degradation, indicating that the impact of myokines may extend beyond inflammatory arthritis to include degenerative joint diseases as well.<sup>56</sup>

While most adipokines promote inflammation and contribute to obesity and metabolic diseases, myokines generally have the opposite effect, benefiting metabolism and reducing inflammation.<sup>55</sup> Myokine production is primarily regulated by physical activity and muscle contraction.<sup>57</sup> Contracting muscles release myokines like IL-6, IL-15, and irisin, which positively influence adipocyte metabolism. Recent studies have emphasized the impact of physical inactivity on the immune system and the risk of exacerbating autoimmune diseases.<sup>58,59</sup> Regular physical activity leads to significant changes in immune system function, such as increased production of regulatory T cells. Moreover, physical activity reduces immunoglobulin production and shifts the balance between T helper cells type 1 (Th1) and T helper cells type 2 (Th2) toward a decrease in Th1 cells.<sup>60</sup> Physical exercise, including both aerobic and resistance training, affects both the innate and adaptive immune systems. The innate system responds to physical activity with increased blood neutrophil counts and



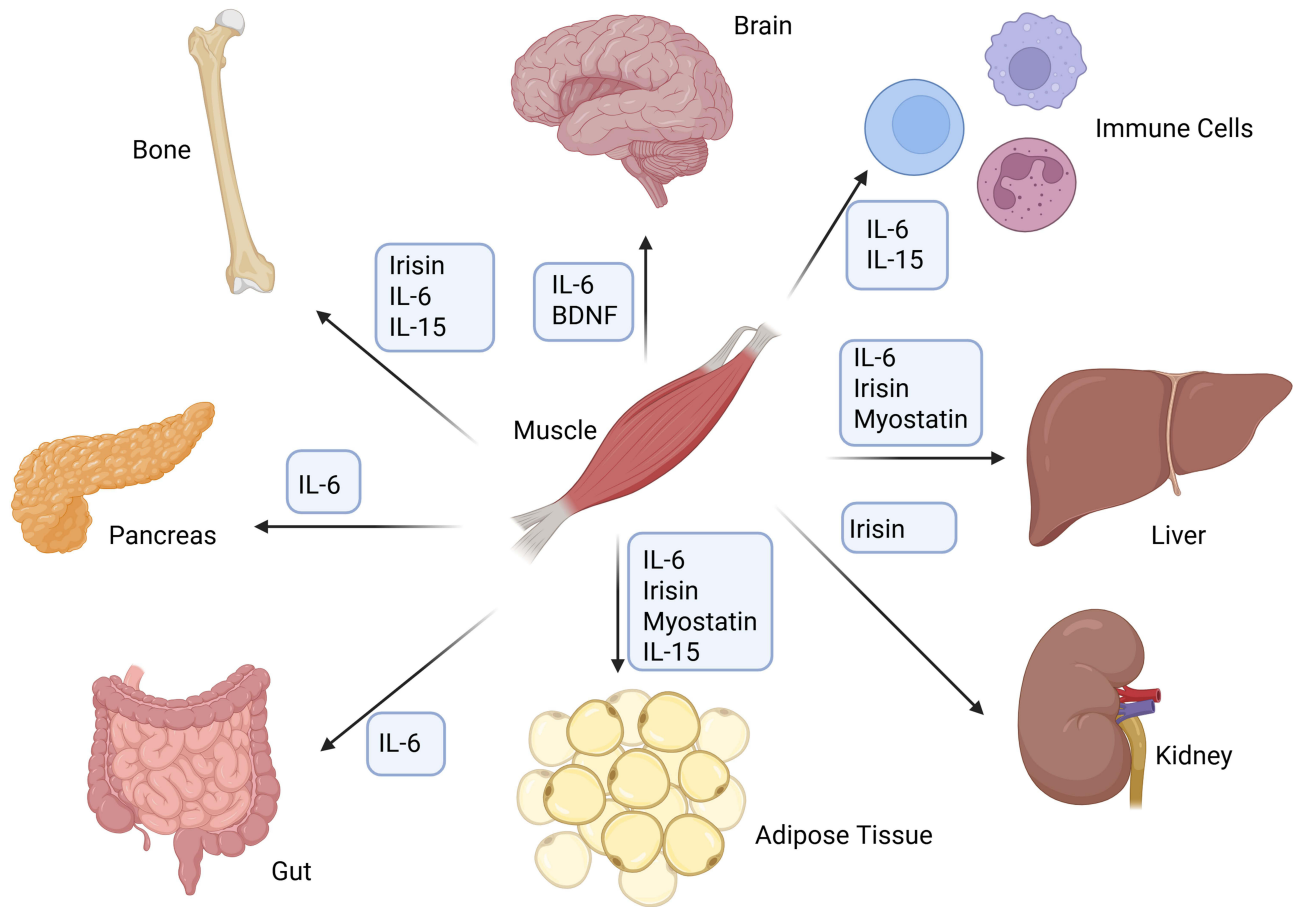
**Figure 1** The impact of physical exercise and myokines on the central nervous system (arrows pointing upward indicate an increase; arrows pointing downward indicate a decrease).

a temporary rise in monocytes, dendritic cells, and natural killer cells.<sup>61</sup> These changes support short-term inflammatory responses and immune cell mobilization, enhancing the body's ability to fight infections and respond to stressors. Regular exercise can thus positively influence immune function, improving its response to threats.<sup>62</sup> The immune system response to exercise depends on the duration and intensity of the activity. Previous studies described immune system changes, such as shifts in immune cell populations, under intense exercise (ie, exceeding 60% of maximum oxygen uptake and heart rate reserve for over an hour). More recent research has shown, that even less intense, shorter activity benefits the entire body, including the immune system.<sup>63</sup> Moderate exercise enhances macrophage activity and improves the circulation of key immune components like antibodies, anti-inflammatory cytokines, and white blood cells (neutrophils, natural killer (NK) cells, cytotoxic T lymphocytes, and immature B lymphocytes).<sup>64</sup> Populations of different white blood cells respond differently to acute physical exercise. Neutrophil counts increase during and after exercise, whereas lymphocyte numbers increase during exercise but decrease below baseline after prolonged exercise. A single moderate exercise session promotes immune cell mobilization, especially those with a more differentiated phenotype and cytotoxic properties, such as NK cells, CD8+ T lymphocytes,  $\gamma\delta$  T lymphocytes, CD16- monocytes, and CD16- neutrophils.<sup>65</sup> Physical exercise also affects subsets of mononuclear blood cells, increasing the concentrations of various lymphocyte subpopulations such as CD4+ T cells, CD8+ T cells, CD19+ B cells, CD16+ NK cells, and CD56+ NK cells. The CD4/CD8 ratio decreases due to a greater increase in CD8+ lymphocytes. Both CD4+ and CD8+ cells include memory (CD45RO+) and naïve (CD45RA+) lymphocytes; however, exercise primarily recruits CD45RO+ memory lymphocytes. Recent studies suggest, that memory lymphocytes, rather than naïve lymphocytes, are rapidly mobilized into the bloodstream during exercise.<sup>66–68</sup> Leukocytes mobilized by physical exercise exhibit increased expression of integrins, intracellular adhesion molecules, and a broad range of chemokine receptors (eg, CXC chemokine receptor (CXCR) 2, 3, and 5).<sup>65</sup> Intense physical activity enhances the expression of C-C chemokine receptor type 5 (CCR5) on monocytes and T lymphocytes. This increase leads T lymphocytes to produce higher levels of the anti-inflammatory cytokine interleukin 10 (IL-10), suggesting that elevated CCR5 expression on leukocytes helps reduce inflammation.<sup>69</sup>

Muscle contraction and damage activate resident immune cells, such as monocytes and macrophages leading to the release of chemokines, attracting neutrophils, and creating a pro-inflammatory environment. This cytokine-dominated milieu, characterized by interferon gamma (IFN- $\gamma$ ) and TNF- $\alpha$ , draws additional macrophages from the bloodstream into muscle tissue. Newly recruited macrophages, known as M1 macrophages, promote inflammation, whereas M2 macrophages support anti-inflammatory processes and muscle repair.<sup>62</sup> As M1 macrophages transition to the M2 type, the levels of the anti-inflammatory cytokine IL-10 increase. IL-10 modulates inflammation by facilitating the M1-to-M2 shift and supports muscle regeneration after injury by signaling satellite cells to differentiate and repair damaged tissues.<sup>70</sup> On the other hand, IFN- $\gamma$  influences the production of pro-inflammatory M1 macrophages and regulates the expression of the Class II Major Histocompatibility Complex Transactivator (CIITA) gene in muscle cells.<sup>71</sup> During physical exercise, stress hormones like adrenaline and cortisol increase. Adrenaline binds to beta-adrenergic receptors on immune cells (T lymphocytes, NK cells, macrophages, and neutrophils), activating G proteins and increasing intracellular cyclic adenosine monophosphate (cAMP) levels.<sup>72</sup> Activation of the cAMP pathway controls pro-inflammatory cytokine production and leukocyte recruitment.<sup>73</sup> Cortisol increases in plasma after physical exercise.<sup>74</sup> This increase is associated with IL-6 production and depends on exercise intensity and duration. Prolonged exercise can lead to cortisol-mediated immune suppression, contributing to higher neutrophil counts and lower lymphocyte counts.<sup>75</sup> IL-6 is one of the first cytokines to appear in the circulation during physical exercise. The absence of an increase in other pro-inflammatory cytokines during exercise suggests that the activation of cytokine cascades is distinct from that triggered by infection. Physical exercise also increases the level of anti-inflammatory cytokines and cytokine inhibitors such as interleukin-1 receptor antagonist (IL-1RA), IL-10, and soluble tumor necrosis factor receptor (sTNF-R).<sup>17</sup> As illustrated in [Figure 2](#), selected myokines exert systemic effects on various organs, highlighting their role in muscle–organ communication relevant to inflammatory joint diseases. Additionally, [Table 1](#) presents the role of selected myokines in RA.

## Myokines and Their Impact on Fatigue

In chronic inflammatory diseases, fatigue arises from a complex interplay between the immune and nervous systems, orchestrated by pro-inflammatory cytokines.<sup>83</sup> During inflammation, cytokines like TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 can cross



**Figure 2** Muscle-derived myokines and their target organs.

the blood-brain barrier. However, inflammation can disrupt the blood-brain barrier integrity, allowing cytokines to enter the brain. Once inside the brain, cytokines trigger “sickness behavior”, characterized by fatigue, malaise, and other symptoms.<sup>84</sup> This response prioritizes the body’s fight against inflammation, diverting energy away from non-essential functions.<sup>85</sup> Inflammation can activate microglia, disrupting the barrier and increasing its permeability.<sup>86</sup> Certain brain regions have capillaries with small openings that allow some cytokines to pass through. The signaling molecule TNF- $\alpha$  can also alter the blood-brain barrier structure, increasing its permeability.<sup>87</sup> Finally, immune cells

**Table 1** The Role of Selected Myokines in RA

| Myokine   | Primary Signaling Pathways                   | Target Cells/<br>Tissues                    | Main Functions                                                     | Association with RA                                                                                                                                 |
|-----------|----------------------------------------------|---------------------------------------------|--------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| IL-6      | JAK/STAT3, MAPK                              | Hepatocytes,<br>immune cells, CNS           | Pro- and anti-inflammatory;<br>fatigue modulation                  | Abundant in RA synovial fluid/serum and correlates with<br>activity and joint damage <sup>76</sup>                                                  |
| IL-15     | JAK/STAT, PI3K/AKT                           | NK cells, T cells,<br>muscle cells          | Enhances immune function and<br>muscle metabolism                  | Elevated IL-15: in the serum in RA; <sup>77</sup> higher risk of<br>severe course in early RA; <sup>77</sup> in synovial fluid in RA; <sup>78</sup> |
| BDNF      | TrkB receptor, PI3K/AKT, MAPK                | Neurons, muscle<br>tissue                   | Neuroplasticity, fatigue and<br>mood regulation                    | High BDNF in severe RA and decreases with anti-TNF<br>therapy <sup>79</sup>                                                                         |
| Irisin    | AMPK, PGC-1 $\alpha$ , Wnt/ $\beta$ -catenin | Adipose tissue,<br>neurons,<br>chondrocytes | Promotes neurogenesis,<br>cartilage protection, browning<br>of fat | Reduced irisin levels in RA; <sup>80</sup> Reduced irisin is linked to<br>sarcopenia and osteoporotic fractures in RA <sup>80</sup>                 |
| Myostatin | SMAD2/3 (TGF- $\beta$ family)                | Muscle cells,<br>synovium                   | Inhibits muscle growth,<br>promotes catabolism                     | Elevated myostatin in RA; <sup>81</sup> Myostatin predicts joint<br>damage, synergistic with myopenia in RA <sup>82</sup>                           |

within the brain can produce cytokines locally, contributing to neuroinflammation due to microglia and astrocytes activation.<sup>88</sup>

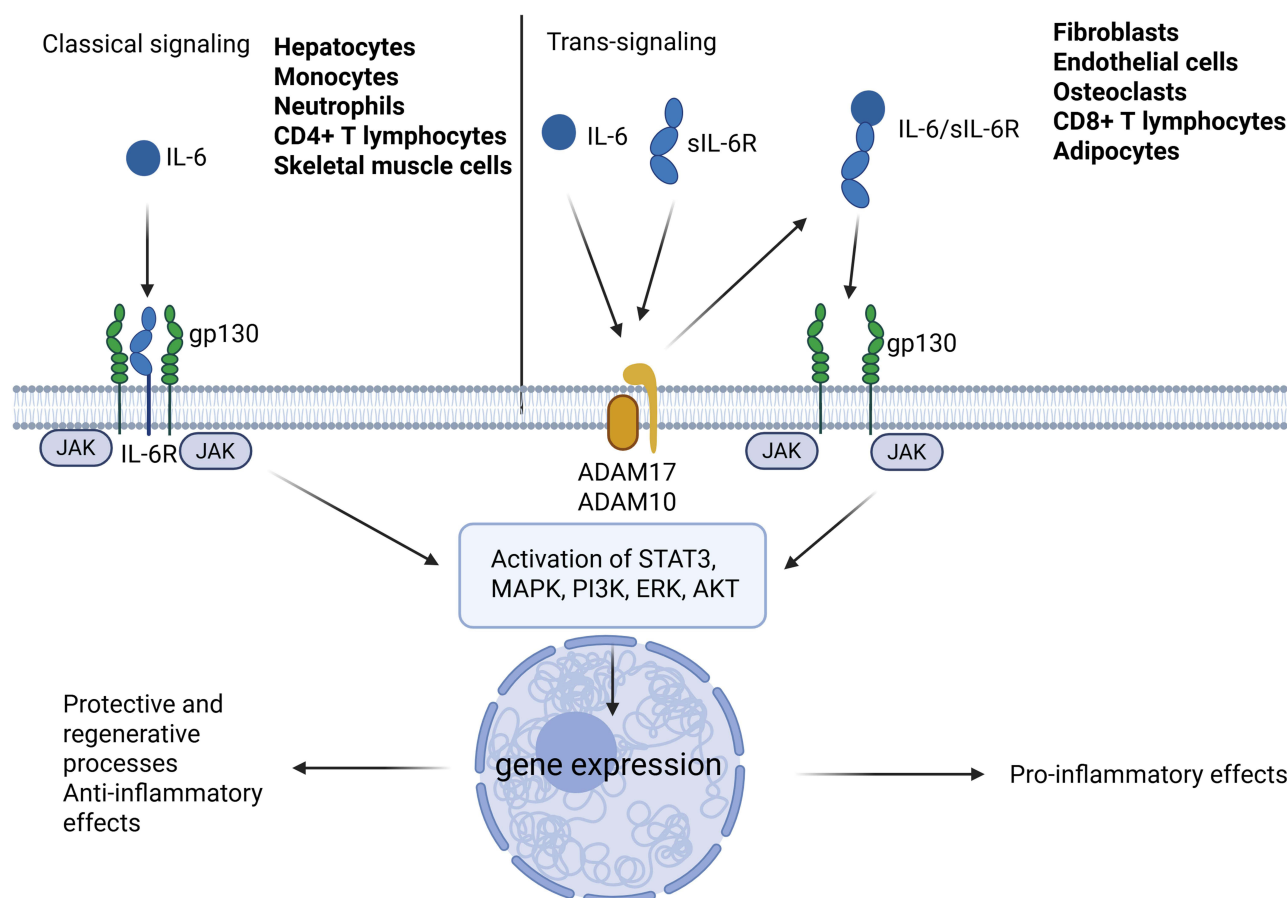
This intricate communication between the immune system, cytokines, and the brain highlights the complex interplay underlying fatigue in chronic inflammatory diseases. The brain and immune system are intricately connected, with inflammation capable of spreading from the body to the brain through both chemical and nerve pathways.<sup>89</sup> While locally produced cytokines in the brain can diffuse and activate nearby immune cells, perpetuating inflammation, a separate “neural pathway” also exists.<sup>90</sup> This pathway involves afferent nerve fibers, originating in organs like the gut and lungs, which carry inflammatory signals directly to a brain region called the nucleus tractus solitarius (NTS). The NTS acts as a central hub, receiving inflammatory signals from both the body and the bloodstream. This dual activation amplifies the inflammatory message within the brain. The NTS also projects signals to other brain areas involved in sleep and fatigue.<sup>91</sup>

The activation of the immune system triggers a cascade of events that ultimately lead to the development of fatigue and its associated symptoms.<sup>92</sup> The communication between muscles and the central nervous system (CNS) involves myokines, metabolites, bioactive lipids, enzymes, and exosomes.<sup>93</sup> Myokine-mediated muscle-CNS communication influences complex behaviors and body functions, impacting mood, sleep, and neurotransmitter production, highlighting the brain’s dependence on muscle-originating signals.<sup>94</sup> Myokines also regulate appetite, aligning food intake with muscle energy demands. A lack of physical activity and muscle atrophy can disrupt this communication, altering myokine production and potentially impairing brain function.<sup>93</sup> Physical exercise exerts a protective effect on the central nervous system, slowing aging and protecting against diseases. Physical activity may help prevent age-related cognitive decline and Alzheimer’s disease by supporting neuronal and vascular plasticity.<sup>95</sup> When discussing the role of myokines in inflammatory joint diseases, it is essential to consider the frequent presence of comorbidities such as obesity, type 2 diabetes mellitus, cardiovascular disease, and depression. These conditions may significantly influence circulating levels of both pro- and anti-inflammatory myokines. Obesity significantly alters the secretion and function of myokines, contributing to a shift toward a pro-inflammatory and metabolically unfavorable profile. Circulating levels of beneficial myokines such as irisin, IL-15, BDNF are often reduced in individuals with obesity, impairing muscle–adipose tissue communication and exacerbating fatigue, insulin resistance, and low-grade inflammation. In contrast, the expression of catabolic and pro-inflammatory factors such as myostatin and adipose-derived IL-6 is elevated, promoting muscle wasting and further disrupting metabolic homeostasis.<sup>21,96</sup> Type 2 diabetes mellitus leads to distinct alterations in myokine secretion patterns due to chronic hyperglycemia, insulin resistance, and skeletal muscle dysfunction. The alterations in myokine concentrations in T2DM closely resemble those observed in obesity, given the high rate of co-occurrence and the shared metabolic and inflammatory pathways. Additionally, T2DM is associated with elevated levels of myostatin, which suppresses muscle growth and exacerbates insulin resistance.<sup>97</sup> A growing body of evidence suggests that various myokines—including myostatin, irisin, BDNF, mitsugumin 53 (MG53), meteorin-like protein (Metrl), apelin (AP), follistatin-like 1 (FSTL1), decorin (DCN), and myogenin—play important roles in modulating the development and progression of cardiovascular diseases. Quantifying the levels of these myokines in peripheral blood may offer new opportunities for understanding CVD pathophysiology and assist clinicians in stratifying patients according to their cardiovascular risk.<sup>98</sup> Myokine levels are influenced not only by comorbid conditions but also by pharmacological treatments, which may either suppress or enhance their expression depending on the drug class and mechanism of action. Glucocorticoids contribute to muscle wasting by activating several catabolic pathways that impair both muscle mass and function. They upregulate the production of catabolic myokines, including myostatin, while simultaneously suppressing anabolic myokines such as insulin-like growth factor 1 (IGF-1). Moreover, glucocorticoids can induce resistance to IGF-1 signaling, further exacerbating muscle degeneration and functional decline.<sup>99</sup> Antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine or sertraline, have been shown to influence BDNF levels and potentially irisin expression through modulation of the hypothalamic–pituitary–adrenal axis.<sup>100</sup>

## Interleukin-6

The first identified myokine was IL-6.<sup>101</sup> Steensberg et al demonstrated that contracting skeletal muscles during prolonged single-leg exercise released significant amounts of IL-6.<sup>102</sup> This finding, confirmed by numerous studies, revealed the substantial impact of muscle-derived IL-6 on metabolism.<sup>38,103</sup> Currently, IL-6 is considered a pleiotropic cytokine with complex roles and effects.<sup>104</sup> It is regarded as a primary pro-inflammatory cytokine involved in both acute-phase processes and chronic inflammatory.<sup>105</sup> IL-6 is the principal cytokine in the IL-6 superfamily, which includes interleukin-11 (IL-11), interleukin-27 (IL-27), interleukin-31 (IL-31), leukemia inhibitory factor, ciliary neurotrophic factor, oncostatin M, cardiotropin-1, neuropoietin, and cardiotropin-like cytokine.<sup>106</sup> Cytokines belonging to this family share a common beta receptor—the membrane glycoprotein gp130—while each has its own specific alpha receptor (IL-6R). Both the IL-6R alpha and gp130 receptors are part of the type I cytokine receptor family, which also includes receptors for prolactin, growth hormone, many interleukins, leptin, erythropoietin, thrombopoietin, leukemia inhibitory factor, oncostatin M, ciliary neurotrophic factor, and granulocyte colony-stimulating factor.<sup>107</sup> To transmit signals to the cell, IL-6 binds to its alpha receptor (also known as gp80 or CD126) leading to the dimerization of two gp130 molecules (also known as the IL-6 signal transducer or CD130) forming a hexamer. Only this receptor complex structure can convey an IL-6-dependent signal. This process activates Janus kinase/signal transducer and activator of transcription molecules, leading to the activation of transcription factors for various genes.<sup>108</sup> This type of signaling is referred to as classical signaling. IL-6 also has a soluble receptor (sIL-6R). When IL-6 binds to this soluble receptor, a complex is formed that can bind to gp130 on cells that do not express membrane-bound IL-6R. This type of signaling is called trans-signaling and expands the range of cells in which IL-6 can act.<sup>109</sup> The formation of sIL-6R is mediated by proteases, primarily disintegrin and metalloproteinase 17 (ADAM17), but also by a disintegrin and metalloproteinase 10 (ADAM10), rhomboid family member 2, cathepsin S, meprin  $\alpha$ , and meprin  $\beta$ .<sup>110</sup> Depending on which pathway is activated—classical or trans-signaling—IL-6 exerts different effects on cells and tissues. All cytokines in the IL-6 family transmit signals into the cell through the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway.<sup>101</sup> Activation through the classical pathway contributes to anti-inflammatory effects and occurs mainly in leukocytes and liver cells. Trans-signaling can enable IL-6 to transmit signals to all cells expressing gp130 and is responsible for inducing pro-inflammatory effects.<sup>111</sup> Binding of IL-6 to the membrane or soluble receptor and to gp130 leads to the activation of signaling pathways through the signal transducer and activator of transcription 3 (STAT3), mitogen-activated protein kinase (MAPK), and phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathways, which phosphorylate STAT3, extracellular regulated kinase (ERK), and Akt, respectively. Phosphorylated STAT3 (pSTAT3) and Akt (pAkt) are important signaling proteins in inflammatory responses, while pAkt is believed to play an important role in cell survival and phosphorylated ERK (pERK) is critical for cell proliferation, which is an important process involved in angiogenesis. IL-6 trans-signaling is responsible for initiating pSTAT3 and pAkt, serving as markers for pro-inflammatory signaling, while IL-6 classic signaling drives the activation of the Akt and ERK pathways, which are indicative of pro-angiogenic signaling responses.<sup>112</sup> Activation of the classical IL-6 signaling pathway (via the membrane-bound receptor) stimulates protective and regenerative processes, whereas activation via the soluble receptor (trans-signaling) has pro-inflammatory effects and can affect a broader range of cells. Classical IL-6 signaling leads to intestinal cell proliferation, inhibition of apoptosis, defense against bacterial infections, and IL-6-dependent regeneration in tissues like the liver, pancreas, and intestine. The pro-inflammatory effects of IL-6 trans-signaling include recruitment of myeloid cells, stimulation of endothelial and smooth muscle cells, inhibition of T cell apoptosis, and inhibition of regulatory T cell differentiation.<sup>110</sup> For visual clarity, Figure 3 presents a diagram of the IL-6 classical and trans-signaling pathways. Recently, another signaling pathway for IL-6 has been described: cluster signaling. In cluster signaling, the IL-6/IL-6R complex on one cell activates the gp130 subunit on a neighboring cell.<sup>113</sup>

Healthy individuals typically have very low levels of IL-6 in their blood (approximately 1–5 pg/mL). However, soluble forms of the IL-6 receptor (sIL-6R) and gp130 (sgp130) are found at much higher concentrations (25–75 ng/mL and 400 ng/mL, respectively).<sup>114</sup> During disease or inflammation, IL-6 levels can rise, exceeding 100 ng/mL. High levels of sIL-6R and sgp130 can act as a buffer system, either enhancing IL-6 activity by forming IL-6/sIL-6R complexes or inhibiting it by forming IL-6/sIL-6R/sgp130 complexes. Studies suggest that despite the high concentrations of sIL-6R



**Figure 3** Mechanisms of IL-6 signaling: classical vs trans-signaling pathways.

and sgp130, there is still enough free IL-6 in the blood to enable both classical IL-6 signaling and the alternative pathway involving sIL-6R.<sup>115–117</sup> The classical IL-6 signaling pathway is dominant in contracting skeletal muscles. IL-6 is rapidly released from contracting muscle fibers, and its concentration depends on the duration and intensity of the contraction, as well as the decrease in muscle glycogen levels. IL-6 improves postprandial glycemia by delaying gastric emptying, increasing glucose uptake, and promoting lipid mobilization and oxidation, reducing the risk of metabolic disorders.<sup>75</sup> IL-6 facilitates communication between muscles and other organs to maintain muscle energy homeostasis.<sup>118</sup> IL-6 plays a crucial role in muscle homeostasis and the activation of satellite cells, which are responsible for muscle regeneration. Maintaining muscle cell homeostasis requires an optimal IL-6 concentration.<sup>119</sup> In genetically modified mice lacking IL-6, muscle hypertrophy is reduced due to impaired satellite cell proliferation.<sup>120</sup> While slightly elevated IL-6 levels appear to benefit muscle tissue, chronically elevated levels lead to muscle atrophy during aging and disease.<sup>119</sup> Wedell-Neergaard et al demonstrated that IL-6 is necessary for exercise-induced reduction of adipose tissue. In their study, obese patients treated with the IL-6 inhibitor tocilizumab did not experience a reduction in visceral fat after cycling exercises and also showed no improvement in cholesterol levels with exercise.<sup>121</sup>

Elevated IL-6 levels are frequently linked to fatigue in cancer patients, and IL-6 administration in healthy individuals induces sleep disturbances and fatigue. IL-6 blocking drugs like tocilizumab and sarilumab have shown promise in reducing fatigue in various conditions, including inflammatory joint diseases and Parkinson's disease.<sup>122</sup> Current evidence suggests that IL-6, in its myokine role, stimulates the secretion of IL-1RA and IL-10. IL-1RA blocks the activity of the pro-inflammatory cytokine IL-1 $\beta$ , implicated in autoimmune diseases like RA. The increase in IL-6 during physical activity helps mitigate inflammation, including neuroinflammation, which contributes to sickness behavior and fatigue.<sup>60</sup>

## Myostatin

Myostatin (GDF8) is a myokine produced by skeletal muscles that inhibits muscle growth. It is a key regulator of muscle cell proliferation and differentiation, limiting both the number and size of muscle cells. Animals lacking the GDF8 gene exhibit significantly larger skeletal muscles throughout the body, which are often two to three times heavier than those in wild-type animals. This increase in muscle mass results from both hyperplasia and hypertrophy.<sup>123</sup> Beyond its role in muscle growth, myostatin also influences fat and glucose metabolism, adipocyte proliferation, cardiomyocyte homeostasis, and bone metabolism.<sup>124</sup> Research suggests that myostatin may enhance osteoclast differentiation and inflammation, contributing to joint bone loss in RA. Studies have shown elevated myostatin levels in the joints of both RA patients and mouse models of this disease. Higher myostatin levels in RA patients correlate with an increased risk of low muscle mass, cachexia, and myopenia.<sup>125</sup> Myostatin has been shown to increase TNF- $\alpha$  expression in RA synovial fibroblasts via the phosphatidylinositol 3-kinase – protein kinase B – activator protein 1 (PI3K-Akt-AP-1) signaling pathway.<sup>126</sup> It also induces IL-1 $\beta$  production through two mechanisms: the anaplastic lymphoma kinase receptor (ALK receptor), c-Jun N-terminal kinase (JNK), ERK, AP-1 signaling pathways, and by suppressing MicroRNA-21-5p (miR-21-5p).<sup>127</sup> Moreover, myostatin significantly increases osteoclast formation through Mothers against decapentaplegic homolog 2 (SMAD2) and Nuclear Factor of Activated T-cells, cytoplasmic 1 (NFATC1) signaling pathways. Reducing myostatin activity has been shown to alleviate arthritis severity in a mouse model, primarily by protecting against bone damage.<sup>128</sup> In the case of RA, studies indicate a connection between myostatin, muscle loss, and inflammation. It has been observed that higher levels of myostatin are associated with both increased inflammation and decreased muscle mass in patients with RA.<sup>129</sup> Myostatin also appears to play a significant role in the development of cachexia in cancer patients treated with platinum-based drugs.<sup>130</sup> This condition is characterized by muscle wasting, fatigue, and systemic inflammation. The mechanism is still unclear, but it seems that activation of the myostatin pathway may play an important role in this process.<sup>40</sup> Furthermore, cisplatin treatment increases myostatin expression and SMAD2 phosphorylation, contributing to muscle loss. Myostatin binds to activin receptor type-2B (ACVR2B) receptors on muscle cells, leading to the activation of SMAD2/3 transcription factors which in turn affects gene expression related to muscle growth.<sup>131</sup> In a double-blind placebo-controlled trial, Vicia faba hydrolysate (NPN\_1) supplementation improved strength recovery and reduced fatigue after exercise-induced muscle soreness in healthy males. Specifically, NPN\_1 significantly reduced myostatin expression, while also increasing markers related to muscle protein synthesis and regeneration. This finding suggests a potential mechanism by which NPN\_1 may improve muscle recovery and reduce fatigue by modulating myostatin levels and promoting muscle repair processes.<sup>132</sup>

## Interleukin-15

IL-15 is a pro-inflammatory cytokine with diverse functions, linking the innate and adaptive immune systems.<sup>133</sup> It plays a crucial role in defending against intracellular pathogens by stimulating the growth and survival of B cells, T cells, and NK cells by increasing the expression of anti-apoptotic factors and reducing the expression of pro-apoptotic factors, which results in inhibiting apoptosis.<sup>134</sup> It is produced, along with Interleukin-15 receptor alpha (IL-15R $\alpha$ ), by various cell populations, including monocytes, macrophages, dendritic cells, fibroblasts, keratinocytes, and epithelial cells.<sup>135</sup> The IL-15 receptor consists of three subunits: the IL-15 specific IL-15R $\alpha$  subunit, and two subunits shared with the interleukin 2 (IL-2) receptor: interleukin 2 receptor beta (IL-2R $\beta$ ) and the common gamma chain ( $\gamma$ c). This gamma chain is also shared by IL-2, interleukin 4 (IL-4), interleukin 7 (IL-7), interleukin 9 (IL-9), and interleukin 21 (IL-21).<sup>136</sup> The binding of IL-15 to its receptor activates Janus kinase 1 (JAK1) and Janus kinase 3 (JAK3), subsequently activating signal transducer and activator of transcription 5A (STAT5A) and signal transducer and activator of transcription 5B (STAT5B).<sup>137</sup> The IL-15 gene produces two isoforms: a short 21 amino acid form and a long 48 amino acid form. The long form binds intracellularly to IL-15R $\alpha$  within skeletal muscle cells before being secreted. This complex can signal via two methods: trans-presentation (remaining bound to IL-15R $\alpha$  while interacting with the  $\beta$  and  $\gamma$  chains of the IL-2 receptor on target cells) or as a heterodimer (releasing IL-15R $\alpha$  and directly binding to the IL-2 receptor).<sup>138</sup> IL-15 is also classified as a myokine, with its concentration increasing significantly during physical activity, regardless of exercise type or individual training status/body composition.<sup>139</sup> While some studies have yielded conflicting results, the timing of

blood sample collection post-exercise is crucial for accurate IL-15 measurement because of its short half-life (30–60 minutes).<sup>140</sup> IL-15 can stimulate the expression of contractile proteins, leading to hypertrophy of muscle cells.<sup>141</sup> In addition to its immunomodulating role, IL-15 directly impacts bone remodeling processes, supporting the differentiation of preosteoclasts.<sup>142</sup> Additionally, IL-15 increases glucose uptake in muscle cells through the activation of glucose transporter 4 (GLUT-4) via JAK3/STAT3, improving insulin sensitivity. Furthermore, IL-15 produced by skeletal muscles can also communicate with adipose tissue. This communication can lead to reduced fat mass, decreased formation of new fat cells, and lower levels of triglycerides and very-low-density lipoprotein (VLDL) in the bloodstream.<sup>143</sup>

IL-15 plays a complex role in inflammatory processes, which are frequently linked to fatigue. While chronic inflammation is a hallmark of many conditions characterized by fatigue, the precise contribution of IL-15 to fatigue development remains to be fully elucidated. Reduced plasma IL-15 levels have been linked to chronic fatigue syndrome in women.<sup>144</sup> However, further research examining IL-15 in cerebrospinal fluid has yielded conflicting results, with one study showing no significant difference in concentration.<sup>145</sup> Further research is needed to understand the specific mechanisms by which IL-15 may contribute to fatigue in the context of inflammatory conditions.

## Brain-Derived Neurotrophic Factor

BDNF, a member of the neurotrophin family is a crucial mediator of neuronal plasticity. It influences the formation of new synaptic connections, enables CNS regeneration, and slows neurodegeneration.<sup>146</sup> High BDNF concentrations are found in brain regions like the hippocampus, cerebral cortex, midbrain, thalamus (amygdala), hypothalamus, striatum, pons, and medulla oblongata, as well as in the peripheral nervous system. Decreased BDNF levels in elderly individuals may be a marker for memory disorders and cognitive decline.<sup>147</sup> BDNF is produced via post-translational modification of its precursor (proBDNF), which is stored in axons or dendrites and converted to mature BDNF both intracellularly and extracellularly.<sup>148</sup> Both BDNF and its precursor, proBDNF, are biologically active, although BDNF's activity is substantially greater.<sup>149</sup> The proteins bind to at least two cell surface receptors: tropomyosin receptor kinase B and the p75 neurotrophin receptor (p75NTR). BDNF exhibits a higher affinity for tropomyosin receptor kinase B (TrkB), leading to protective and anti-apoptotic effects upon activation. Conversely, proBDNF preferentially binds to p75NTR, initiating neurodegenerative processes and apoptosis.<sup>146</sup> BDNF binding to TrkB activates three intracellular signaling pathways: PI3K/AKT, Ras/MEK/MAPK/ERK, and PLC $\gamma$ /DAG/IP3. These pathways contribute to neuronal survival, neurogenesis, and the development of neuronal projections.<sup>150</sup> Furthermore, BDNF-TrkB binding can activate cAMP-response element-binding protein (CREB), which subsequently increases the production of the c-fos and JunD genes, which are crucial for neurogenesis and neuronal survival.<sup>151</sup> Numerous studies have highlighted the crucial role of BDNF in regulating N-methyl-D-aspartate receptor (NMDAR) transport, phosphorylation, and expression levels. BDNF also contributes to increasing the number, size, and complexity of dendritic protrusions.<sup>148</sup> These processes, which enhance neuronal lifespan, promote new neuronal connections and increase synapse numbers, are essential for memory formation and learning. Elevated BDNF levels are associated with improved cognitive function and mental health in both healthy individuals and those with depression.<sup>152</sup> Many scientists have demonstrated that physical activity leads to an increase in the expression and secretion of BDNF in the brain.<sup>153–155</sup> The mechanisms responsible for the increase in BDNF levels during physical exercise are still being studied. Three main pathways have been identified. The first involves the hemodynamic response, where increased shear stress in the endothelial cells of blood vessels during exercise leads to BDNF synthesis dependent on nitric oxide. The second mechanism is the neuronal pathway, in which BDNF levels increase as a result of neuronal activity. The third pathway, a recently discovered pathway, involves the connection between muscles and the central nervous system. Contracting skeletal muscles release myokines that enter the bloodstream and travel to the central nervous system, facilitating communication between these two organs.<sup>156</sup> The level of circulating BDNF in the blood may reflect its brain concentration. Studies indicate that 70–80% of the serum BDNF in humans, both at rest and during exercise, originates from the brain.<sup>149</sup> Decreased BDNF levels are observed in neurodegenerative and psychiatric diseases like Alzheimer's disease, depression, and schizophrenia.<sup>157</sup> Physical exercise significantly increases BDNF levels in both healthy individuals and Alzheimer's disease patients.<sup>158</sup> BDNF also plays a crucial role in regulating energy balance, which is controlled by BDNF-expressing neurons in the periventricular

hypothalamus. Mice lacking the BDNF gene exhibit hyperphagia, reduced activity, impaired thermogenesis, and severe obesity. BDNF neurons in the anterior periventricular hypothalamus regulate energy intake and physical activity, whereas those in the medial and posterior regions promote thermogenesis by releasing BDNF into the spinal cord, increasing sympathetic nervous system activity.<sup>159</sup> BDNF also acts as a myokine, and is secreted by contracting skeletal muscles, influencing muscle fiber differentiation. The absence of BDNF expression increases free muscle fibers and resistance to contraction-induced fatigue, while BDNF overexpression increases fast-twitch, glycolytic fibers.<sup>160</sup> In skeletal muscle, BDNF helps maintain muscle function, strengthens neuromuscular junctions during exercise, regulates beta-oxidation and glucose uptake, and influences muscle regeneration.<sup>161</sup>

BDNF can also influence behavior and fatigue.<sup>162</sup> The BDNF Val66Met polymorphism, a substitution of valine with methionine at codon 66, can lead to changes in brain structure and memory-related processes, although its clinical significance remains unclear. The three genotypes are Val/Val (wild type), Val/Met (heterozygote), and Met/Met (homozygote). A mouse model (BDNFMet/Met) mirroring the human phenotype shows normal BDNFMet expression but impaired neuronal secretion. Under stress, these mice exhibit increased anxiety-like behaviors resistant to antidepressants like fluoxetine, suggesting a potential link between the BDNF variant and anxiety/depressive disorders.<sup>163</sup> However, research is inconclusive. Studies have shown that Val/Met may lower cancer-related fatigue risk, while Val/Val may increase it.<sup>164</sup> Research on the BDNF Val66Met polymorphism and its effects on cognitive function and mood in cancer patients presents a complex picture. Low baseline BDNF blood levels in cancer patients correlate with poorer attention, memory, and cognitive abilities during treatment.<sup>165</sup> However, cancer patients with the Met/Met genotype demonstrated better executive functions compared to those with the Val/Val genotype.<sup>166</sup> Met allele carriers also showed protection against general subjective cognitive dysfunction related to cancer, especially in memory, multitasking, and verbal skills.<sup>167</sup> Conversely, studies from 2010 suggested that Met alleles increase depression risk in men.<sup>168</sup> Sex-related differences further complicate the relationship between the BDNF Val66Met polymorphism and cancer-related fatigue. Male cancer patients without depression who carry the Met allele (Met/Met or Val/Met) report less cancer-related fatigue than those with the Val/Val genotype.<sup>164</sup> Conversely, female cancer patients with Met/Met genotypes experience greater fatigue and neuropathic pain compared to other genotypes.<sup>169</sup> Studies in both animal and human models indicate that the Met allele (Val/Met, Met/Met) contributes to reduced hippocampal volume, dendritic complexity, and simplified spatial arrangement.<sup>170</sup> Sex-related differences further complicate the relationship between the BDNF Val66Met polymorphism and cancer-related fatigue. Male cancer patients without depression who carry the Met allele (Met/Met or Val/Met) report less cancer-related fatigue than those with the Val/Val genotype.<sup>164</sup> Conversely, female cancer patients with Met/Met experience greater fatigue and neuropathic pain compared to other genotypes.<sup>169</sup> Studies in both animal and human models indicate that the Met allele (Val/Met, Met/Met) contributes to reduced hippocampal volume, dendritic complexity, and simplified spatial arrangement.<sup>171</sup> While the Met allele of the BDNF Val66Met polymorphism is linked to negative outcomes like memory impairment and increased anxiety/depression risk, its high prevalence suggests potential evolutionary advantages, particularly in older individuals. Studies indicate that Met allele carriers may have greater cortical thickness, better episodic memory, slower cognitive decline, and lower Alzheimer's disease risk later in life, although not in early adulthood.<sup>172,173</sup>

The relationship between BDNF and fatigue is highly complex, as alterations in BDNF concentration do not consistently correlate with improvements in fatigue symptoms.<sup>174</sup>

In patients with RA, reduced BDNF levels have been observed in those experiencing depression, with a significant inverse correlation between BDNF concentration and depressive symptom severity as measured by the Korean version of the Beck Depression Inventory-II (K-BDI II). Depression in RA has been linked to increased fatigue, reduced BDNF expression, and higher disease activity, all of which contribute to a diminished ability to perform daily functional tasks.<sup>175</sup> In another study, researchers reported that baseline and post-exercise serum BDNF levels were comparable between RA patients and healthy controls. Although both groups demonstrated a significant decrease in BDNF levels following aerobic exercise, the magnitude of change ( $\Delta$ BDNF) was significantly greater in the RA group. Furthermore, in RA patients,  $\Delta$ BDNF levels showed a significant association scores on the Hospital Anxiety and Depression Scale, a relationship not observed in the control group.<sup>176</sup> Similarly, in study involving patients with multiple sclerosis (MS), lactate threshold training resulted in a significant increase in BDNF levels, which was accompanied by a reduction in

fatigue symptoms. However, this beneficial effect was not sustained at long-term follow-up, suggesting that while exercise-induced BDNF elevation may temporarily alleviate fatigue, its long-term impact remains limited.<sup>177</sup> Collectively, these findings support the role of BDNF as a dynamic, though possibly transient, biomarker of fatigue in rheumatic diseases, particularly in the context of neuropsychiatric comorbidities and therapeutic interventions such as exercise.

## Irisin

Irisin, a polypeptide myokine discovered in 2012, is released by skeletal muscles in response to muscle contraction during physical exercise.<sup>178</sup> It is formed through proteolytic cleavage from the membrane protein fibronectin type III domain-containing protein 5 (FNDC5). Skeletal muscle contraction during physical activity increases the transcription of peroxisome proliferator-activated receptor gamma co-activator (PGC-1 $\alpha$ ), resulting in the expression of FNDC5, from which irisin is derived.<sup>179</sup> Irisin unique dimeric structure distinguishes it from other proteins with a fibronectin type III domain, enhancing its function as a ligand.<sup>180</sup> Irisin expression has been observed in various tissues beyond skeletal muscles, including heart muscle, Purkinje cells in the cerebellum, skin, pancreas, spleen, and stomach.<sup>181</sup> One of the first described functions of irisin was the induction of white adipose tissue browning and its impact on thermogenesis through increased expression of uncoupling protein 1 (UCP1).<sup>178</sup> Furthermore, irisin is involved in the regulation of energy expenditure, glucose uptake, and glycogenolysis, while inhibiting gluconeogenesis, fat formation, and lipid accumulation. It also has a potentially beneficial effect on glucose balance and insulin sensitivity.<sup>182</sup> Irisin regulates the function of osteoclasts, osteoblasts, and osteocytes.<sup>183</sup> The levels of this myokine decrease with age and in bone diseases, including primary and secondary osteoporosis.<sup>184</sup> It has been shown that a single session of exercise involving whole-body vibration can increase the irisin level in the blood, but regular training with this method does not appear to affect irisin levels at rest.<sup>185</sup> Irisin is present throughout the brain, particularly in the cerebellum, cortex, hippocampus, nucleus accumbens, and hypothalamus and it appears to be essential for proper brain function and is linked to neurodegenerative diseases.<sup>186</sup> Irisin activates signaling pathways related to energy metabolism, including PGC-1 $\alpha$ , and those related to memory formation, such as BDNF, which are involved in depression.<sup>187</sup> Recent research suggests that irisin plays a beneficial role in neurological disorders by regulating energy metabolism, enhancing synaptic plasticity, supporting neurogenesis, reducing neuroinflammation, and inhibiting oxidative stress.<sup>188</sup> One study revealed that aerobic exercise increased blood irisin levels in multiple sclerosis patients, correlating with improvements in depression, cognitive performance, and fatigue.<sup>189</sup> In mice, short-term subcutaneous irisin administration showed antidepressant and anxiolytic effects, potentially via activation of the Pgc-1 $\alpha$ /FNDC5 pathway in the brain.<sup>190</sup> Moderate to high-intensity exercise can significantly up-regulate the level of serum irisin, which regulates bone and cartilage metabolism through a complex mechanism. Irisin not only activates osteogenic differentiation through the activation of Wnt/ $\beta$ -catenin and adenosine monophosphate-activated protein kinase (AMPK) pathways but also enhances osteoblastic transcription regulators such as osterix and Runt-related transcription factor 2 (RUNX2).<sup>56</sup> These findings are further supported by a study in which weekly irisin administration in mice for a month demonstrated antidepressant and anxiolytic effects, likely due to changes in brain factors. Irisin treatment increased neurotrophic gene expression, including BDNF and IGF-1, exclusively in treated mice brains. Additionally, irisin influences the expression of several cytokines, including IL-1 $\beta$ , IL-4, IL-6, and IL-10.<sup>191</sup> Human studies corroborate these findings, showing lower irisin blood levels in individuals with post-stroke depression compared to those without, with irisin being a stronger predictor than age or serotonin levels.<sup>192</sup> Irisin's neuroprotective effects stem from its ability to reduce neuroinflammation and act as an antioxidant.<sup>188</sup>

## Future Perspectives

There is increasing recognition of myokines as pivotal mediators of muscle–organ crosstalk, reflecting their systemic biological roles and growing therapeutic potential. Research efforts have thus shifted toward developing strategies that modulate myokine pathways to treat chronic inflammatory and metabolic conditions, including inflammatory joint diseases. In the coming years, pharmacological modulation of myokines is expected to complement or substitute for exercise-based interventions, particularly in patients with limited mobility or severe disease activity. In both RA and osteoarthritis, such approaches aim to reproduce or potentiate the anti-inflammatory and fatigue-alleviating effects of

exercise-induced myokines. A recent study demonstrated that nicorandil, a cardiovascular agent, can significantly reduced immobilization-induced joint capsule fibrosis and arthrogenic contracture by suppressing RhoA/ROCK and TGF- $\beta$ 1/Smad signaling. Although nicorandil's action is primarily antifibrotic, this finding highlights how pharmacologic agents may indirectly modulate muscle–joint crosstalk and pathways related to myokine signaling, suggesting novel avenues for therapeutic intervention.<sup>193</sup> In parallel, advances in extracellular vesicle (EV) biology offer a promising platform for targeted delivery of regenerative signals. EVs - nanoscale particles secreted through paracrine mechanisms have shown therapeutic potential in cartilage repair, particularly those derived from mesenchymal stem cells, which are enriched in growth factors and signaling molecules involved in chondrogenesis. Experimental studies have demonstrated their ability to promote chondrocyte proliferation and extracellular matrix synthesis. Moreover, the regenerative efficacy can be enhanced through preconditioning or by modifying the cellular source of the EVs.<sup>194</sup> This nanocarrier may serve as precise delivery systems to modulate the joint microenvironment, with potential applications in restoring disrupted muscle–joint communication in rheumatic disorders. Emerging physical therapies such as extracorporeal shock wave therapy (ESWT) have also shown beneficial effects on muscle regeneration and joint pathology. Although myokines were not directly assessed in these studies, ESWT-induced modulation of inflammatory mediators and tissue remodeling factors suggests that it may influence muscle-derived signaling pathways. Therefore, ESWT—used alone or as an adjunct to exercise—may represent an innovative approach to modulate the muscle–joint axis and improve clinical outcomes in patients with inflammatory joint diseases.<sup>195,196</sup> Finally, recent developments in biomaterials have enabled the design of injectable stimuli-responsive hydrogel-based drug delivery platforms that hold promise for improving osteoarthritis treatment. These systems are engineered to release therapeutic agents in response to local biochemical cues (eg, pH, enzymatic activity, reactive oxygen species), thereby enhancing drug bioavailability, tissue specificity, and overall therapeutic efficacy. Integration of such smart hydrogel systems with myokine-targeted therapies could yield synergistic benefits and represents a compelling direction for future research.<sup>197</sup>

## Conclusion

Myokines, once considered mere byproducts of muscle contraction, have emerged as crucial mediators of the complex interplay between physical activity, muscle function, and systemic health, including the intricate experience of fatigue. This exploration into the world of myokines has illuminated their diverse roles, ranging from modulating inflammation and immune responses to influencing metabolism, neuroendocrine function, and even cognitive processes. While the precise mechanisms by which myokines contribute to fatigue are still being unraveled, the evidence points towards a multifaceted picture. The association between inflammatory myokines like IL-6 and fatigue underscores the importance of understanding the inflammatory component in fatigue development, particularly in chronic diseases. Conversely, the potential of exercise-induced myokines to mitigate fatigue through anti-inflammatory and neuroprotective pathways offers promising avenues for therapeutic interventions. Further research is warranted to fully elucidate the intricate network of myokine interactions, their specific contributions to different types of fatigue, and the potential for targeted interventions. This knowledge will be instrumental in developing effective strategies to combat fatigue and improve overall well-being in both healthy individuals and those facing chronic health challenges. Unlocking the full therapeutic potential of myokines holds the promise of revolutionizing our approach to fatigue management and promoting a healthier, more active future. Importantly, the heterogeneous nature of fatigue across individuals calls for a shift toward personalized medicine approaches guided by individual myokine expression profiles. Tailoring therapeutic strategies to the specific myokine signatures of patients may enhance the effectiveness of interventions, improve fatigue management, and promote overall well-being in both healthy individuals and those with chronic conditions. Unraveling the full therapeutic potential of myokines could revolutionize fatigue treatment and support a more targeted, individualized approach to health care.

## Abbreviations

ACVR2B, Activin Receptor Type-2B; ADAM17/ADAM10, A Disintegrin And Metalloproteinase 17/10; AKT, Protein kinase B; ALK, Anaplastic Lymphoma Kinase; AMP, Adenosine monophosphate; AMPK, Adenosine monophosphate-activated protein kinase; AP, Apelin; BDNF, Brain-derived neurotrophic factor; CCR5, C-C chemokine receptor type 5; CD16, Cluster of differentiation 16; CD19, Cluster of differentiation 19; CD4/CD8, Clusters of differentiation 4 and 8;

CD45RO/CD45RA, Clusters of differentiation 45RO and 45RA; CD56, Cluster of differentiation 56; CIITA, Class II Major Histocompatibility Complex Transactivator; CNS, Central nervous system; CREB, cAMP-response element-binding protein; CVD, Cardiovascular diseases; CXCR, CXC chemokine receptors; DAG, Diacylglycerol; DAMPs, Damage-associated molecular patterns; DAS-28, Disease Activity Score-28; DCN, Decorin; ERK, Extracellular Signal-Regulated Kinase; ESWT, Extracorporeal shock wave therapy; EV, Extracellular vesicle; FNDC5, Fibronectin type III domain-containing protein 5; FSTL1, Follistatin-like 1; GDF8, Growth Differentiation Factor 8; GLUT-4, Glucose transporter type 4; IFN- $\gamma$ , Interferon gamma; IGF-1, Insulin-like growth factor 1; IL-10, Interleukin-10; IL-11, Interleukin-11; IL-15, Interleukin-15; IL-15R $\alpha$ , Interleukin-15 Receptor alpha; IL-1, Interleukin-1; IL-1RA, Interleukin-1 receptor antagonist; IL-1 $\beta$ , Interleukin 1 beta; IL-21, Interleukin-21; IL-27, Interleukin-27; IL-2, Interleukin-2; IL-2R $\beta$ , Interleukin-2 Receptor beta; IL-31, Interleukin-31; IL-4, Interleukin-4; IL-6, Interleukin-6; IL-6R, Interleukin-6 receptor; IL-7, Interleukin-7; IL-9, Interleukin-9; IP3, Inositol trisphosphate; JAK/STAT, Janus Kinase/Signal Transducer and Activator of Transcription; JAK1, Janus kinase 1; JAK3, Janus kinase 3; JNK, c-Jun N-terminal Kinases; K-BDI II, Korean version of the Beck Depression Inventory-II; LPS, Lipopolysaccharide; M1/M2 macrophages, M1 and M2 macrophages; MAMPs, Metabolism-associated molecular patterns; MAPK, Mitogen-Activated Protein Kinase; MEK, Mitogen-activated protein kinase kinase; MG53, Mitsugumin 53; MS, Multiple sclerosis; Met, Methionine; Metrnl, Meteorin-like protein; NFATC1, Nuclear Factor of Activated T-cells, cytoplasmic 1; NK cells, Natural killer cells; NMDAR, N-methyl-D-aspartate receptor; NOD, Nucleotide-binding oligomerization domain; NPN\_1, Vicia faba hydrolysate; NTS, Nucleus tractus solitaries; PAMPs, Pathogen-associated molecular patterns; PGC-1 $\alpha$ , Peroxisome proliferator-activated receptor gamma co-activator 1 alpha; PI3K-Akt-AP-1, Phosphatidylinositol 3-kinase – Protein Kinase B – Activator Protein 1; PI3K/Akt, Phosphatidylinositol 3-Kinase/Protein Kinase B; PI3K, Phosphatidylinositol 3-kinase; PLC $\gamma$ , Phospholipase C gamma; PRRs, Pattern recognition receptors; Pgc-1 $\alpha$ /FNDC5, Peroxisome proliferator-activated receptor gamma co-activator 1 alpha / Fibronectin type III domain-containing protein 5 pathway; RA, Rheumatoid arthritis; Ras, Rat sarcoma viral oncogene homolog; SMAD2, Mothers Against Decapentaplegic Homolog 2; SSRIs, Selective serotonin reuptake inhibitors; STAT3, Signal Transducer and Activator of Transcription 3; STAT5A, Signal Transducer and Activator of Transcription 5A; STAT5B, Signal Transducer and Activator of Transcription 5B; T2DM, Type 2 diabetes mellitus; TNF-alpha, Tumour necrosis factor alpha; Th1/Th2, T helper cell type 1 and type 2; TrkB, Tropomyosin receptor kinase B; UCP1, Uncoupling protein 1; VLDL, Very-low-density lipoprotein; Val, Valine; cAMP, Cyclic adenosine monophosphate; gp130/CD130, Glycoprotein 130 / Cluster of Differentiation 130; gp130, Glycoprotein 130; gp80/CD126, Glycoprotein 80 / Cluster of Differentiation 126; miR-21-5p, microRNA-21-5p; ng/mL, nanograms per millilitre; p75NTR, p75 neurotrophin receptor; pSTAT3/pAkt/pERK, phosphorylated STAT3/Akt/ERK; pg/mL, picograms per millilitre; proBDNF, precursor of Brain-derived neurotrophic factor; sIL-6R, Soluble Interleukin-6 Receptor; sTNF-R, Soluble tumour necrosis factor receptors; sgp130, soluble glycoprotein 130;  $\gamma$ c, Common gamma chain;  $\gamma\delta$  T lymphocytes, Gamma delta T lymphocytes.

## Author Contributions

All authors made substantial contributions to the conception, literature review, and interpretation of the data; participated in drafting, revising, or critically reviewing the manuscript; approved the final version to be published; agreed on the journal to which the article has been submitted; and accept responsibility for all aspects of the work.

## Funding

This study was funded by the Minister of Science under the Regional Initiative of Excellence Program.

## Disclosure

The authors declare that they have no conflicts of interest in this work.

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