

The Application Potential of the Regulation of Tregs Function by Irisin in the Prevention and Treatment of Immune-Related Diseases

Zhengjiang Wang^{1,2,*}, Jiaqi Xu^{1,2,*}, Liquan Mo¹, Renshu Zhan^{1,2}, Jin Zhang^{1,2}, Li Liu^{1,2}, Jun Jiang^{1,2}, Yingying Zhang^{1,2}, Yiping Bai^{1,2}

¹Department of Anesthesiology, The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan Province, 646000, People's Republic of China; ²Anesthesiology and Critical Care Medicine Key Laboratory of Luzhou, Southwest Medical University, Luzhou, Sichuan Province, 646000, People's Republic of China; ³Department of Pharmacology and Toxicology, University of Mississippi Medical Center, Jackson, MS, 39216, USA; ⁴Department of General Surgery (Thyroid Surgery), The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan Province, 646000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yingying Zhang; Yiping Bai, Email yingyingzhang917@gmail.com; baiyiping0608@163.com

Abstract: Irisin is a muscle factor induced by exercise, generated through the proteolytic cleavage of the membrane protein fibronectin type III domain-containing protein 5 (FNDC-5). Numerous studies have shown that irisin plays a significant role in regulating glucose and lipid metabolism, inhibiting oxidative stress, reducing systemic inflammatory responses, and providing neuroprotection. Additionally, irisin can exert immunomodulatory functions by regulating regulatory T cells (Tregs). Tregs are a highly differentiated subset of mature T cells that play a key role in maintaining self-immune homeostasis and are closely related to infections, inflammation, immune-related diseases, and tumors. Irisin exerts persistent positive effects on Treg cell functions through various mechanisms, including regulating Treg cell differentiation and proliferation, improving their function, modulating the balance of immune cells, increasing the production of anti-inflammatory cytokines, and enhancing metabolic functions, thereby helping to maintain immune homeostasis and prevent immune-related diseases. As an important myokine, irisin interacts with receptors on the cell membrane, activating multiple intracellular signaling pathways to regulate cell metabolism, proliferation, and function. Although the specific receptor for irisin has not been fully identified, integrins are considered potential receptors. Irisin activates various signaling pathways, including AMPK, MAPK, and PI3K/Akt, through integrin receptors, thereby exerting multiple biological effects. These research findings provide important clues for understanding the mechanisms of irisin's action and theoretical basis for its potential applications in metabolic diseases and immunomodulation. This article reviews the relationship between irisin and Tregs, as well as the research progress of irisin in immune-related diseases such as multiple sclerosis, myasthenia gravis, acquired immune deficiency syndrome, type 1 diabetes, sepsis, and rheumatoid arthritis. Studies have revealed that irisin plays an important role in immune regulation by improving the function of Tregs, suggesting its potential application value in the treatment of immune-related diseases.

Keywords: irisin, FNDC5, regulatory T cell, immunity, immune-related diseases

Introduction

Irisin is a glycosylated type I membrane protein, a cleavage product of fibronectin type III domain-containing protein 5 (FNDC5), and is highly homologous between humans and mice.¹⁻⁴ Recent studies have shown that irisin plays a significant role under various physiological and pathological conditions, including promoting bone remodeling,⁵ improving the prognosis of metabolic diseases,^{3,6} and exhibiting anti-inflammatory,^{7,8} anti-oxidative stress, anti-apoptotic,^{5,6,9} neuroprotective,^{7,10} and organ ischemia-injury protective effects.⁹ Multiple studies have indicated that irisin can enhance the function of natural killer cells and play various roles in immune regulation. Irisin significantly

inhibits the pro-inflammatory polarization of microglia and macrophages by reducing the expression of pro-inflammatory factors and promotes the transition of macrophages to the anti-inflammatory M2 type. Regarding neutrophils, irisin exerts anti-inflammatory effects by inhibiting their infiltration and the formation of extracellular traps, thereby reducing inflammation and tissue damage. Additionally, irisin can inhibit the activity and expression of T lymphocytes and various inflammatory factors.^{8,11–15} Overall, irisin is primarily endogenously produced by skeletal muscle cells but can also be obtained exogenously in research and potential therapeutic applications. By directly regulating the function of immune cells and improving metabolism, reducing inflammation, and combating oxidative stress, irisin shows great therapeutic potential in immune-related diseases. Regulatory T cells (Tregs) are a highly differentiated subset of mature T cells characterized by the expression of CD4+CD25+Foxp3+ on their surface. These cells interact with various cells of the innate and adaptive immune systems and are closely associated with multiple diseases and disorders, including infections, inflammation, immune-related diseases, and tumors.^{16–19} Dysfunction of Tregs is closely related to multiple sclerosis (MS), myasthenia gravis (MG), acquired immune deficiency syndrome (AIDS), type 1 diabetes mellitus (T1DM), sepsis, and rheumatoid arthritis (RA). Currently, there are few reviews on the regulation of Tregs function by irisin for the treatment of immune-related diseases. This article reviews the relationship between irisin and Tregs in immune-related diseases and evaluates the potential application of irisin in regulating Tregs function for the prevention and treatment of immune-related diseases. It is hoped that by sorting and discussing the existing literature, this review will provide a reference for further research.

Irisin, Tregs, and MS

Irisin and MS

Multiple sclerosis is an immune-mediated inflammatory and neurodegenerative disease that manifests as a multi-focal demyelination of the central nervous system (CNS).^{20,21} Studies have shown that elevated levels of inflammatory cytokines, such as interleukin (IL)-17 and IL-1 β , play an important role in the pathogenesis and progression of MS.^{22–28} In the pathogenesis of MS, oxidative stress is considered a key factor, leading to cellular dysfunction, demyelination, and neuronal death. During the progression of MS, oxidative damage is particularly significant,^{28–30} and it has been suggested that irisin might directly act on neurons, relating to the pathological process of MS. This may involve protective effects on neurons, as well as mitigation of demyelination and axonal damage.³¹ Irisin can improve symptoms in MS patients, and by increasing serum irisin levels, improvements in depression, cognitive abilities, and fatigue symptoms in MS patients have been observed.^{32,33} This could be related to irisin's impact on neuroprotection, inflammation reduction, oxidative stress, and apoptosis.^{34,35} Moreover, exercise is known to increase irisin levels. In animal model studies of neuroautoimmune diseases, exercise has been shown to reduce oxidative stress, inhibit the production of inflammatory cytokines, and modulate the immune response by promoting the activity of regulatory T cells. The studies also indicate that exercise, by altering the expression of adhesion molecules and enhancing the tight junctions in spinal cord tissue, helps to restore the integrity of the blood-brain barrier (BBB), limiting the migration of autoreactive T cells into the central nervous system.³⁶ This is significant for the treatment of MS, as T cell infiltration is closely associated with MS exacerbations, and irisin, as a hormone secreted after exercise, may play an indispensable role in this process.

Tregs and MS

Regulatory T cells (Tregs) play a crucial role in controlling autoimmune inflammation in the central nervous system, and their dysfunction is considered to be a key factor in the progression of Multiple Sclerosis (MS).^{37,38} Tregs typically regulate peripheral immune responses by suppressing effector T cells (Teffs). When the function of Tregs is compromised, uncontrolled Teffs may attack the myelin sheath, leading to neuronal damage and neuroinflammation.^{28,38,39} Studies have shown that restoring the functional homeostasis of Tregs can alleviate the severity of the disease and help prevent or slow down the development of Experimental Autoimmune Encephalomyelitis (EAE), an animal model of MS.^{40,41} Therefore, restoring the homeostasis of Tregs has been proposed as a potential therapeutic strategy for treating MS, demonstrating promising research prospects.^{42–44}

Irisin, Tregs, and MS

In the blood and cerebrospinal fluid of MS patients, as well as in animal models of multiple sclerosis, research indicates that although the number of Tregs is elevated, their function is impaired, leading to increased susceptibility to the disease and disruption of the autoimmune regulatory process.^{36–38} This phenomenon highlights the importance of Tregs in maintaining immune balance. In preclinical models, supplementation with irisin therapy has shown the potential to alleviate the severity of MS. The mechanisms may include reducing inflammatory responses, alleviating oxidative stress, and inhibiting apoptosis. These effects may be achieved by enhancing the function of Tregs, thereby reducing the pathological activity of effector T cells (Teff) (Figure 1). Specifically, irisin may improve the regulatory capacity of Tregs on immune responses, decrease the release of inflammatory mediators, and protect neurons from immune attacks.

Despite these findings providing a theoretical foundation for irisin as a treatment component for MS, its practical clinical application still faces numerous challenges. These challenges include determining effective and safe dosage ranges, addressing potential side effects, and evaluating the impact of long-term treatment. Additionally, the bioavailability of irisin and its plasma half-life are critical parameters that require special attention in future clinical research. Future research efforts should focus on elucidating the direct impact mechanisms of irisin on Tregs cell function and validating its efficacy and safety in clinical trials. This will involve in-depth studies on the effects of irisin under different dosages and administration regimens, as well as its safety and tolerability in long-term use. Through these studies, a more

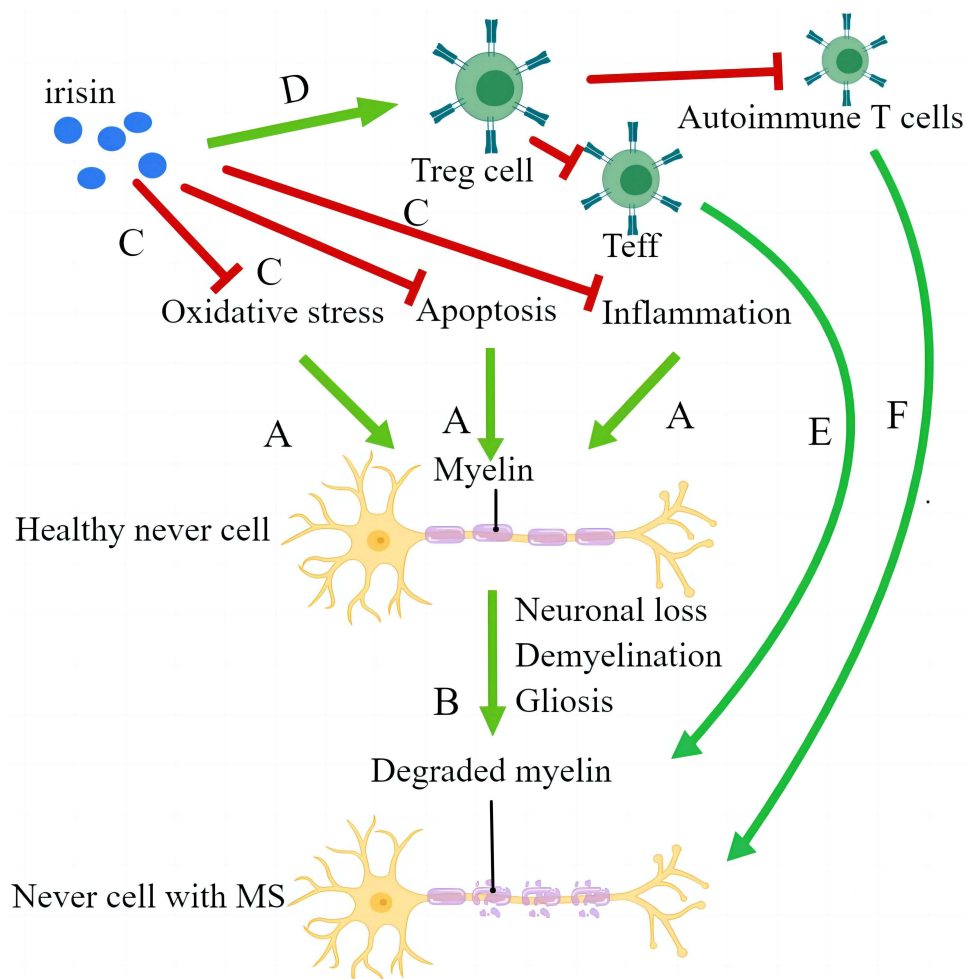


Figure 1 Multiple sclerosis (MS) presents with multifocal demyelination of the central nervous system (A and B). Irisin improves MS by improving demyelination caused by inflammation, oxidative stress, and apoptosis, as well as reducing neuronal loss and glial cell formation caused by axonal injury (C). At the same time, irisin may treat MS by improving Tregs function (D) and inhibiting myelin destruction caused by Teff (effector CD8+ T cells) (E) and autoimmune T cell migration to the CNS (central nervous system) (F).

accurate assessment of irisin's potential in MS treatment can be made, and feasible treatment strategies can be formulated.

Irisin, Tregs, and MG

Irisin and MG

Myasthenia gravis is an autoimmune disease in which autoantibodies attack the acetylcholine receptors (AChR) in skeletal muscles, which leads to impaired transmission at the neuromuscular junctions.^{45–47} Clinical manifestations of MG include abnormal fatigue, weakness of the affected transverse muscles, and an inability to exercise at will, with a temporary reduction or disappearance of symptoms after rest or taking anticholinesterase drugs.⁴⁸ Recent studies have shown that the development and progression of MG are closely associated with the activities of inflammatory mediators and inflammatory cytokines.^{49–52} In contrast, irisin may enhance mitochondrial function and maintain a homeostatic intracellular redox status by promoting an increase in the proportion of Tregs and inhibiting the activation of endoplasmic reticulum-related stress in macrophages. Due to differences in sample selection, heterogeneity of study design, and variation in baseline status, there is controversy regarding the levels of irisin in the serum of patients with myasthenia gravis (MG).^{53,54} Despite these controversies, studies suggest that irisin can reduce the secretion of various inflammatory cytokines. In autoimmune diseases like MG, the anti-inflammatory effects may be beneficial. Irisin may alleviate immune-mediated damage at the neuromuscular junction by reducing the secretion of inflammatory cytokines on one hand, and on the other hand, it may indirectly enhance muscle function and endurance by improving energy metabolism. Additionally, it may regulate the immune system, affecting the function of T cells and other immune cells, improving the autoimmune response, and ameliorating MG.^{53–55}

Tregs and MG

Tregs dysfunction in patients with MG is often associated with elevated levels of pro-inflammatory cytokines, and accordingly, the maintenance of Tregs immune homeostasis may be beneficial for the prognosis of patients with this condition.^{56–60} In this regard, it has been found that thymectomised patients with MG have higher levels of circulating Tregs and enhanced immunoregulation, which, by reducing the expression of AChR antibodies and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), can contribute to a significant improvement in the symptoms of MS.^{61–63} To further validate the role of Tregs in improving MG, Aricha et al⁶⁴ and Sheng et al⁶⁵ adoptively transferred Tregs to mice with experimental autoimmune MG (EAMG) and found that whereas there were reductions in the pro-inflammatory cytokines IL-6, IL-17, and IFN- γ , this treatment promoted increases in the levels of FoxP3 and IL-10. Moreover, reductions were detected in the number of self-reactive T cells and the levels of AChR antibodies, thereby providing evidence that the activity of Tregs can contribute to significant retardation in disease progression in mice with EAMG.^{64,65}

Irisin, Tregs, and MG

Irisin may play a role in MG by increasing the proportion of Tregs and reducing the expression of the AChR antibody and cytotoxic T lymphocyte-associated protein 4 (CTLA-4), as well as the secretion of various inflammatory factors, resulting in improved MG through anti-inflammatory effects⁵⁵ (Figure 2). Although current approaches to treating MG do not target Tregs, a modest increase in Tregs has been found with drugs that do not target Tregs (pyridostigmine, rituximab, azathioprine, intravenous immunoglobulin). In addition, study has discovered that Irisin may ameliorate the immunopathological process of MG by modulating the proportion of Treg cells, which are a type of immune regulatory cell known for their ability to suppress immune responses. Research has found that after stimulating CD4⁺ T cells in MG patients with irisin, the proportion of Treg cells significantly increased, suggesting that irisin may regulate the directional differentiation of Treg cells in MG patients. Additionally, irisin can inhibit the activation of endoplasmic reticulum stress in macrophages, improve mitochondrial function damage, and inhibit the production of intracellular reactive oxygen species, thereby alleviating the inflammatory response. Therefore, we hypothesize that irisin may exert its anti-inflammatory effects in the immune pathogenesis of MG through the following mechanisms: firstly, by increasing the proportion of Treg cells; secondly, by inhibiting the activation of endoplasmic reticulum stress in macrophages;

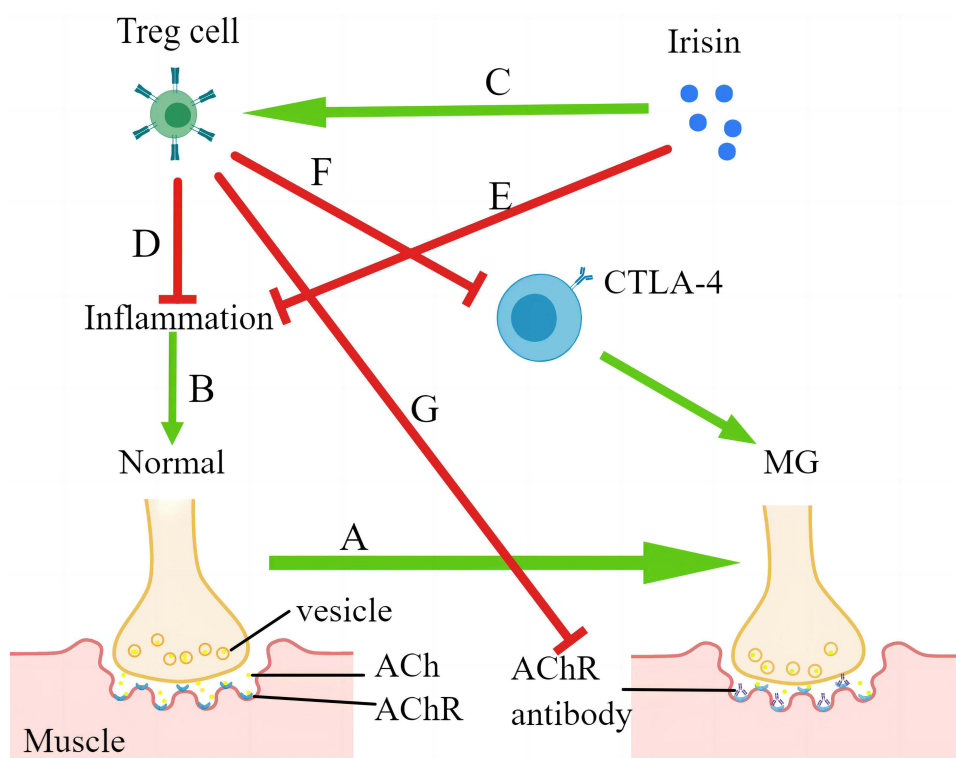


Figure 2 Myasthenia gravis (MG) is an immune-related disease in which autoantibodies attack the skeletal muscle acetylcholine receptor (AChR), resulting in neuromuscular junction transmission disorders (A). Inflammatory mediators and cytokines are closely related to the development of MG (B). Irisin may increase the proportion of Tregs, reduce the expression of the AChR antibody and cytotoxic T lymphocyte-associated protein 4 (CTLA-4), as well as the secretion of various inflammatory factors, and improve MG through anti-inflammatory effects (C-G).

furthermore, by improving mitochondrial function and maintaining the balance of intracellular redox state; and ultimately, by reducing the secretion of inflammatory factors.^{55,56}

Irisin, Tregs, and AIDS

Irisin and AIDS

Acquired immune deficiency syndrome, caused by infection with the human immunodeficiency virus (HIV), is characterised by immunodeficiency and a series of opportunistic infections and tumours, which in severe cases can prove fatal.⁶⁶ Patients with AIDS have been established to have elevated levels of irisin that do not respond to lifestyle modification and are unrelated to brown adipose tissue gene expression,⁶⁷ thereby indicating a possible association between HIV infection and irisin levels. In this regard, Trombetta et al demonstrated a positive correlation between irisin levels and body fat in HIV-infected subjects and a negative correlation with strength parameters.⁶⁸

In the context of HIV infection and its related complications, irisin may exert effects through several mechanisms: Metabolic Regulation, individuals with HIV commonly experience metabolic complications such as insulin resistance and fat redistribution after initiating antiretroviral therapy (ART). Irisin, by enhancing insulin sensitivity and promoting energy expenditure, could help improve these metabolic issues;^{3,6} Anti-inflammatory Action, chronic inflammation in individuals with HIV is associated with an increased risk of non-infectious diseases such as cardiovascular and liver diseases. The anti-inflammatory properties of irisin could help mitigate chronic inflammation, thereby reducing the risk of these complications;^{7,8} Immune Function Modulation, HIV primarily damages the immune system by destroying CD4+ T cells. Irisin might indirectly affect immune regulation and has the potential to improve or support the immune status of individuals with HIV;⁵ Promotion of Muscle Function and Reduction of Wasting Symptoms, individuals with HIV may experience muscle wasting and a decline in strength. Due to its role in enhancing muscle mass and endurance, irisin could be beneficial in improving muscle function and alleviating wasting symptoms in HIV-infected

individuals;^{8,11–15} Neuroprotective Effect, HIV infection can affect the central nervous system and lead to cognitive decline. Although there is limited research on irisin's role in HIV-related neurological issues, its potential neuroprotective effect offers the possibility that irisin might help alleviate HIV-related neurological complications.^{7,10}

It is important to note that these effects and potential benefits are mainly based on findings of irisin in other research areas, and direct studies on HIV infection may still be relatively limited. Therefore, these hypotheses need to be verified through more clinical research specifically targeting individuals with HIV. As research progresses, more biological actions of irisin may be discovered, as well as its practical applications in the treatment and management of HIV.

Tregs and AIDS

The main features characterising the immune system of patients with AIDS are a reduced number and dysfunction of CD4⁺ T lymphocytes,^{69,70} abnormal immune activation,⁷¹ and the restoration of immune integrity in response to antiviral therapy.⁶⁹ Disease progression in these patients is closely associated with inflammation and elevated viral levels,⁷² and even in cases of effective antiviral therapy, patients can continue to experience heightened immune activation and inflammation.⁷³ Consequently, the maintenance of immune homeostasis plays an important role in the treatment of AIDS. In this regard, it has been found that Tregs are positively correlated with HIV viral load and are closely associated with disease progression.^{74–77} However, the suppressive efficacy of Tregs is considered something of a double-edged sword. Suppression occurs primarily in the early stages of acute HIV infection,⁷⁸ during which the amplification of Tregs can contribute to the suppression of immunity, the inhibition of excessive T-cell activation, and a reduction of bodily damage, although it also has the effect of weakening HIV-specific responses and impairing HIV detection and clearance by the body, which tend to be conducive to viral persistence.⁷⁹ Nevertheless, Tregs may play a regulatory role in the protection of HIV hosts and contribute to the specific elimination of HIV,⁸⁰ and thus the maintenance of Tregs functional homeostasis may represent a viable therapeutic approach for treating patients with AIDS.

Irisin, Tregs, and AIDS

Among individuals infected with the HIV virus, persistent immune activation and inflammation are common phenomena that negatively impact treatment effectiveness and the overall health status of the infected person. Against this backdrop, maintaining immune homeostasis becomes particularly important. Irisin, as a potential adjunctive therapy, has the potential to improve the immune function of HIV-infected individuals and alleviate aberrant immune states by enhancing the anti-inflammatory functions of Treg cells (Figure 3). In HIV-related models, boosting the activity of Tregs may help reduce chronic immune activation and levels of inflammation, thereby decreasing HIV replication and disease progression. However, this intervention strategy is not without risks. Enhancing Treg function may improve immune control over HIV infection and reduce damage to the host, but it may also suppress the body's specific immune response to HIV, hampering the recognition and clearance of the virus, and thus leading to its persistent presence.^{78,79} Therefore, when employing Irisin, a delicate balance is needed, possibly requiring dynamic monitoring of HIV load and the host's immune response to determine the optimal timing and dosage of treatment. Future research should focus on the interaction between Irisin and the existing antiretroviral therapy (ART), and whether it can improve the state of immune exhaustion associated with HIV infection. Through these studies, we can gain a deeper understanding of the immunomodulatory mechanisms of Irisin and its potential applications in HIV-infected individuals.

Irisin holds potential value for improving treatment in individuals infected with HIV, and research into its mechanisms and applications in HIV-infected individuals is crucial for developing new strategies to treat HIV/AIDS. The outcomes of future studies will help to reveal the true potential of Irisin in HIV treatment and determine its role in comprehensive treatment regimens. This will provide a more holistic and personalized treatment option for individuals infected with HIV.

Irisin, Tregs, and T1DM

Irisin and T1DM

Type 1 diabetes mellitus generally manifests as a syndrome encompassing a group of metabolic disorders associated with the metabolism of proteins, lipids, and electrolytes associated with the autoimmune-mediated destruction of islet β -cells⁸¹ (Figure 4). It is an inflammatory disease^{82,83} that is mainly characterised by an intense inflammatory response that

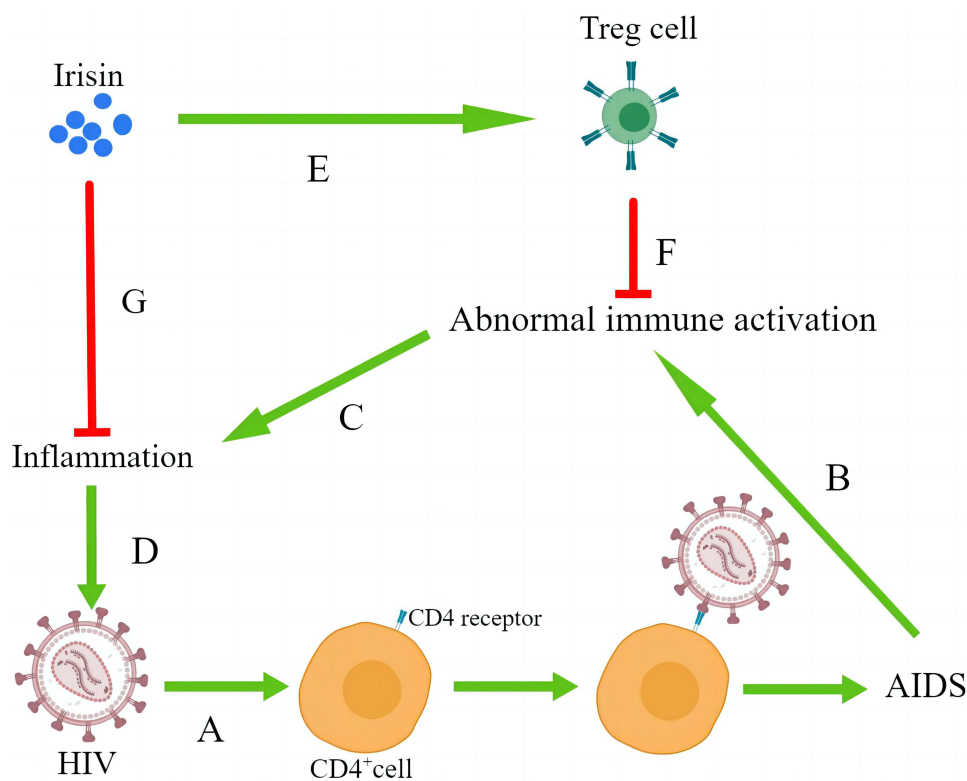


Figure 3 Acquired Immune Deficiency Syndrome (AIDS) refers to immunodeficiency caused by human immunodeficiency virus (HIV) infection (A). The major changes in the immune system of patients with AIDS include a reduced number and dysfunction of CD4⁺ T lymphocytes, abnormal immune activation (B), and inflammation resulting from abnormal immune activation (C). Moreover, the progression of AIDS patients is closely related to increased inflammation and viral levels (D). Irisin may improve abnormal immunity by improving the function of Tregs (E, F) and reducing inflammation (G).

induces T1DM via the lymphocyte-mediated destruction of pancreatic β -cells, followed by a persistent state of systemic low-grade inflammation, and the substantial fluctuation in blood glucose thus induced will exacerbate this inflammation.⁸⁴ In addition to an elevation of inflammatory markers,^{80,81} immune activation^{83,85} and oxidative stress^{86,87} play important roles in the pathogenesis and progression of T1DM.

Observations concerning the association between serum irisin concentrations and T1DM tend to be somewhat inconsistent. Chronic inflammation, autoimmunity, and anti-glutamic acid decarboxylase levels may affect irisin synthesis in patients with T1DM,⁸⁸ however, most patients with T1DM have elevated irisin levels, which is particularly pronounced in women.^{89,90} Moreover, irisin level was negatively correlated with insulin dose in T1DM patients, and irisin could reduce insulin dose⁸⁹ and promote blood glucose control and bone health.⁹⁰ It has been established that exercise can contribute to the production of irisin, and exercise combined with insulin therapy has been found to reduce the associated complications in patients with T1DM and improve their prognosis.⁹¹ Animal studies have also shown that irisin can benefit blood glucose levels by reducing insulin resistance, promoting pancreatic β -cell survival, and enhancing glucose-induced insulin secretion.^{3,92} However, although irisin is generally considered beneficial for the prognosis of patients with T1DM, the change in trends of irisin in patients with T1DM and the specific mechanisms of irisin action need further investigation.

It is important to note that while these mechanisms provide a theoretical hypothesis, the potential therapeutic role and actual mechanisms of action of irisin for T1DM require further research to be confirmed. Current research on irisin primarily focuses on metabolic diseases, particularly Type 2 Diabetes. For Type 1 Diabetes, although irisin may help improve some metabolic parameters, it cannot replace insulin therapy, which is indispensable in the management of T1DM.

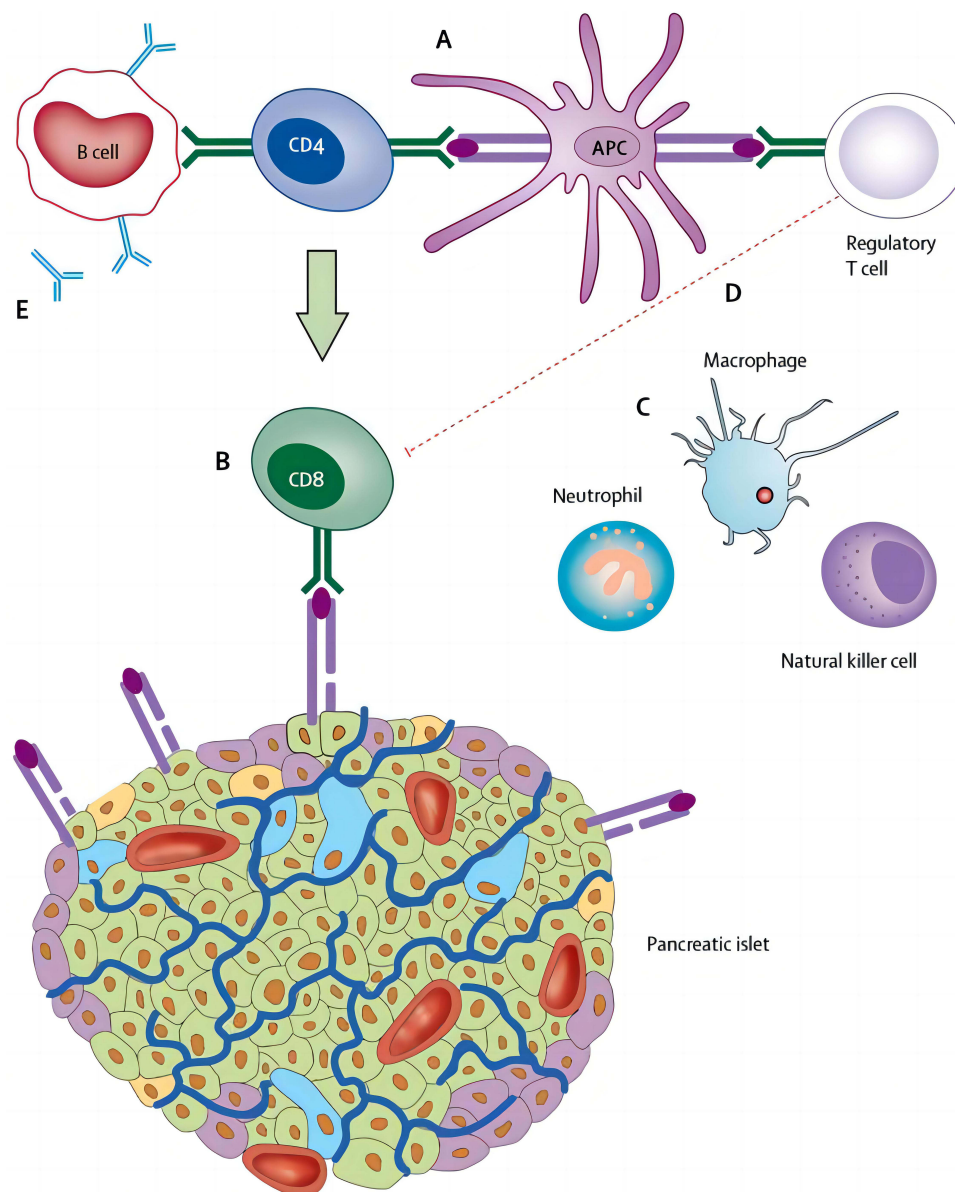


Figure 4 The development of type 1 diabetes is thought to be initiated by the presentation of β -cell peptides by antigen-presenting cells (APCs). APCs bearing these autoantigens migrate to the pancreatic lymph nodes, where they interact with autoreactive $CD4^+$ T lymphocytes, which in turn mediate the activation of autoreactive $CD8^+$ T cells (A). These activated $CD8^+$ T cells return to the islet and lyse β cells expressing immunogenic self-antigens on major histocompatibility complex class I surface molecules (B). β -cell destruction is further exacerbated by the release of proinflammatory cytokines and reactive oxygen species from innate immune cells (macrophages, natural killer cells, and neutrophils) (C). This entire process is amplified by defects in regulatory T lymphocytes, which do not effectively suppress autoimmunity (D). Activated T cells within the pancreatic lymph node also stimulate B lymphocytes to produce autoantibodies against β -cell proteins. These autoantibodies can be measured in the circulation and are considered a defining biomarker of type 1 diabetes (E). Reprinted from The Lancet, Molina C, Oram RA. Type 1 diabetes. *Lancet*. 2018 Jun 16;391(10138):2449–2462. doi: 10.1016/S0140-6736(18)31320-5. from DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. *Lancet*. 2018;391(10138):2449–2462, with permission from Elsevier.⁸¹

Tregs and T1DM

It has been found that the mRNA levels of characteristic Tregs surface molecules and receptors, such as CTLA-4, IL-10 receptor alpha (IL-10 α), TGF- β 1, and TGF- β 2, are generally low in patients with T1DM, as are the levels of signal transducer and activator of transcription 1 (STAT-1) and suppressor of mothers against decapentaplegic 3 (SMAD-3), which are patterns taken to be indicative of impaired Tregs functions in these patients.^{93–95} Moreover, patients with T1DM are generally characterised by a reduced percentage of Tregs.^{96,97} The key to the aetiological treatment of T1DM lies in preventing early islet loss in susceptible individuals, promoting islet regeneration during remission, or islet transplantation in the case of chronic disease, each of which can be regulated by Tregs.⁹⁸ In recent years, animal models

and clinical trials have also confirmed that promoting increases in the number of Tregs in the body, regulate Tregs homeostasis, and improve the progression of T1DM, the effects of which tend to be notably more pronounced during the early stages of T1DM development.^{99,100} However, although this would appear to imply that the activation of Tregs is highly beneficial from the perspective of T1DM treatment,¹⁰⁰ long-term observations in a large number of patients are needed for confirmation.⁹⁹

Irisin, Tregs, and T1DM

The ideal immunotherapy for T1DM should restore self-tolerance without inducing chronic immunosuppression. Irisin is thought to play a significant role in alleviating immune-mediated inflammation. Specifically, irisin may enhance the function of Tregs, thereby reducing the immune system's attack on pancreatic β -cells, alleviating inflammation, and decreasing β -cell damage. Additionally, irisin might protect the remaining pancreatic cells by slowing immune-mediated damage, allowing them to continue producing insulin. The potential benefits of this mechanism include improved metabolic function, better glycemic control in T1DM patients, reduced dependence on insulin injections, and improved clinical outcomes for T1DM. By modulating Tregs function, irisin not only reduces the immune system's attack on the pancreas but may also enhance overall immune regulation, thereby improving patients' health in multiple aspects^{3,90,92} (Figure 5). However, despite these promising mechanisms, the role of irisin in T1DM treatment remains in the research stage. More clinical trials and experimental data are needed to verify the efficacy and safety of these potential mechanisms. Furthermore, the supplementation and regulation of irisin may be influenced by other complex factors, including the patient's lifestyle, genetic background, and disease severity. Therefore, Discussions on irisin as a treatment strategy should be cautious and based on scientific evidence.

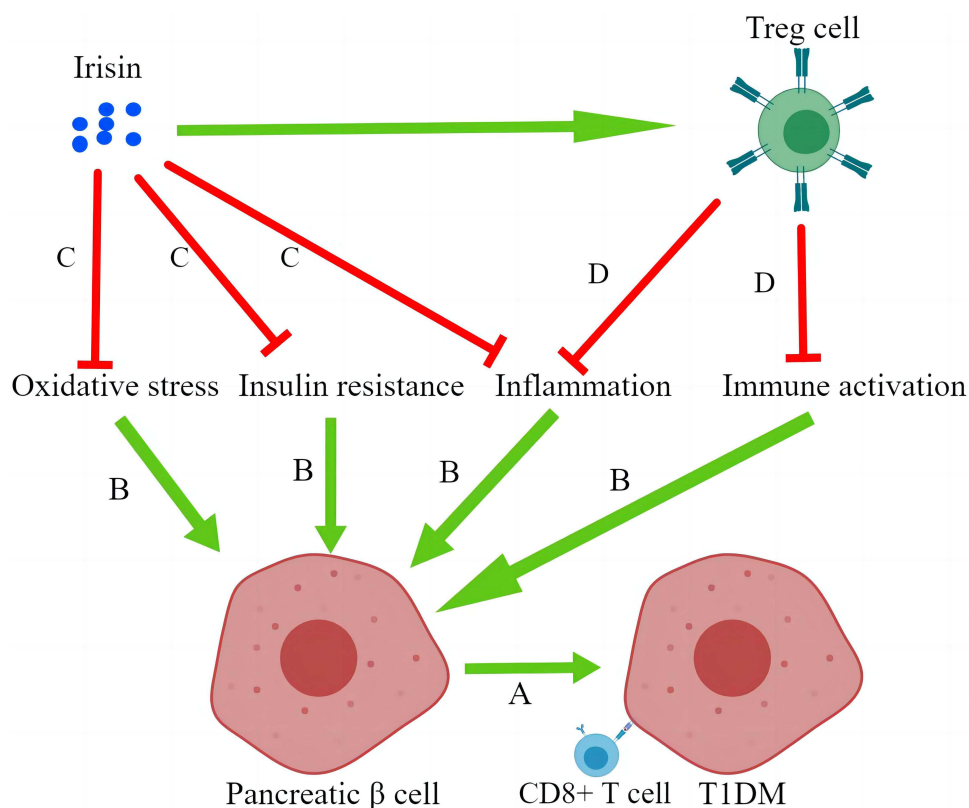


Figure 5 Activated CD8⁺ T cells attack islet β -cells, resulting in type 1 diabetes mellitus (T1DM) (A). Oxidative stress, insulin resistance, inflammation, and immune activation may promote this process (B). Irisin treats T1DM by improving oxidative stress and insulin resistance (C) and promoting Tregs function, reducing inflammation and immune activation (D).

In summary, although the potential of irisin in T1DM treatment is promising, its practical application requires extensive research to confirm its effectiveness and safety. Future studies will help to better understand the role of irisin in immune regulation and T1DM management, leading to the development of more effective treatment strategies.

Irisin, Tregs, and Sepsis

Irisin and Sepsis

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host immune response to infection, characterised by mitochondrial dysfunction, cellular energy exhaustion, and immune dysfunction.^{101–105} Levels of irisin in the serum of patients with sepsis have been demonstrated to be negatively correlated with the severity of sepsis, and given that irisin has been found to ameliorate sepsis and related complications, it is considered to have promising clinical applications.¹⁰⁶

Irisin has been shown to alleviate multiple organ dysfunction syndrome caused by sepsis and may improve sepsis-related cardiac dysfunction via multiple pathways, including blocking the toll-like receptor 4/NLR family pyrin domain containing 3 (TLR4/NLRP3) signalling pathway to inhibit inflammation, apoptosis, and pyroptosis;¹⁰⁷ reducing mitochondrial dysfunction, oxidative stress, and apoptosis via FUN14 domain-containing 1 (FUNDC1)-related mitochondrial autophagy;¹⁰⁸ activating mitochondrial ubiquitin ligase (MITOL) and inhibiting the Gasdermin D (GSDMD)-dependent pyroptosis pathway;¹⁰⁹ regulating the macrophage stimulating 1-c-Jun N-terminal kinase (MST1-JNK) pathway¹¹⁰ and inhibiting the dynamin-related protein 1 (DRP1)-related mitochondrial fission pathway.¹¹¹ Irisin has also been found to ameliorate the symptoms of sepsis-associated encephalopathy by modulating the inflammatory microenvironment via inhibition of ferroptosis in the hippocampus and attenuating neurocognitive dysfunction via an attenuation of blood brain barrier disruption.^{106,112,113} Irisin can improve sepsis-associated alveolar epithelial barrier dysfunction by inhibiting inflammation and apoptosis via the AMP-activated protein kinase/Sirtuin 1 (AMPK/SIRT1) pathway,¹¹⁴ attenuate sepsis-associated liver injury by preventing apoptosis, NLRP3 inflammasome activation, and nuclear factor (NF)- κ B signal transduction,¹¹⁵ and contribute to reducing sepsis-associated acute kidney injury by inhibiting ferroptosis via the SIRT1/nuclear factor erythroid 2-related factor 2 (NRF2) pathway and suppressing inflammation and apoptosis via the NF- κ B pathway.^{113,116} However, despite these ostensibly impressive properties, most of the aforementioned findings pertaining to the therapeutic effects of irisin on sepsis and its complications are based on animal studies. A previous study reported that serum irisin levels decreased in patients with sepsis and were negatively correlated with disease severity,¹¹⁷ highlighting the need for clinical trials to evaluate the use of irisin in patients with sepsis. Insufficient exercise is a risk factor for sepsis death.¹¹⁸ Running can prevent sepsis in mice.^{119–122} Potential protective mechanisms of exercise with sepsis include muscle factors released by muscle contraction. At the same time, exercise can up-regulate the marker products of Tregs, improve the function of Tregs, and reduce the “inflammatory storm”.³⁶ Exercise generally improves skeletal muscle function. Irisin improved the function of Tregs and reduced the “storm of inflammation”, which may be why exercise improved the function of organs with sepsis other than skeletal muscle.^{123,124}

Tregs and Sepsis

In a mouse model of sepsis, a significant increase in the percentage of Tregs was detected 24 h after the initiation of sepsis, with the number and suppressive functions of Tregs increasing more significantly following the onset of septic shock, thereby contributing to a reduction in organ injury and mortality associated with the generation of a cytokine storm.¹²⁵ In this regard, Heuer et al demonstrated a significant increase in the survival of mice with sepsis treated with in vitro stimulation of Tregs proliferation before or after modelling.¹²⁶ Conversely, other studies have provided evidence to indicate that Tregs have no demonstrable effects on the survival of septic model mice^{127,128} and may even reduce survivorship.¹²⁹ It is presumed that these discrepant findings of animal model studies can be attributed to differences in the stage of sepsis, host conditions, and the heterogeneity of Tregs.^{130–133} In related clinical studies, it has been found that the prolonged presence of large numbers of Tregs may be associated with severe immune paralysis, and it has been established that the functional homeostasis of Tregs is more conducive to improving the prognosis of patients with sepsis.^{134–136} Accordingly, continuous monitoring of the changes in Tregs numbers in the peripheral blood of patients

with sepsis would no doubt contribute to evaluating their condition and determining their prognosis. The maintenance of Treg functional homeostasis may thus represent a promising therapeutic strategy for treating patients with sepsis.

Irisin, Tregs, and Sepsis

Irisin, through its diverse biological functions, including anti-inflammatory, antioxidant, metabolic regulation, and organ protection effects, can effectively treat sepsis and its related complications, improving patient prognosis.^{107–116} (Figure 6). The different stages of sepsis, host conditions, and the heterogeneity of Tregs lead to diverse results in animal experiments, suggesting that we may need to more closely monitor and regulate Treg function to achieve immune homeostasis. Therefore, individualized treatment plans and further research are needed to optimize the application of irisin.

Irisin, Tregs, and RA

Irisin and RA

RA's precise aetiology and pathogenesis have yet to be sufficiently elucidated, but it is generally recognised as a chronic systemic autoimmune disease characterised by synovitis. What is known, however, is that extravascular immune

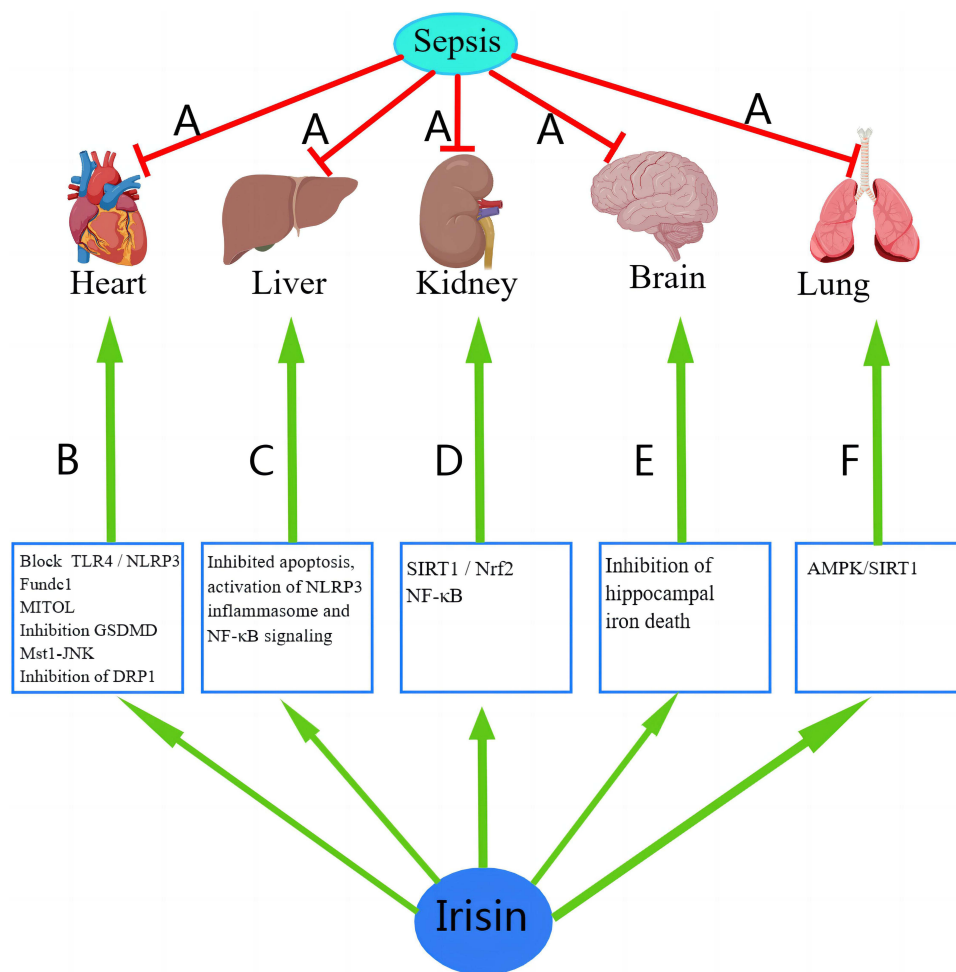


Figure 6 Sepsis can cause multiple organ dysfunctions (A). Irisin can improve sepsis-related cardiac dysfunction in various ways, including by blocking the TLR4/NLRP3 signalling pathway to inhibit inflammation, apoptosis, and pyrodeath and through Funde1-related mitochondrial autophagy. It alleviates mitochondrial dysfunction, oxidative stress, and apoptosis by activating mitochondrial ubiquitin ligase (MITOL), inhibiting the Gasdermin D (GSDMD)-dependent scorch death pathway and DRP1-associated mitochondrial fission pathway, and regulating the Mst1-JNK pathway (B). Irisin reduces sepsis-associated liver damage by suppressing apoptosis, activating the NLRP3 inflammasome, and NF-κB signalling (C). Irisin inhibits iron death through the SIRT1/Nrf2 pathway and inflammation and apoptosis through the NF-κB pathway, reducing sepsis-associated acute kidney injury (D). Irisin improves the inflammatory microenvironment by blocking iron death in the hippocampus, alleviates neurocognitive dysfunction, and promotes SAE by reducing blood-brain barrier disruption (E). Irisin suppresses inflammation and apoptosis through the AMPK/SIRT1 pathway, decreasing sepsis-associated alveolar epithelial barrier dysfunction (F).

complexes form and stimulate an inflammatory response, whereas the release of cytokines associated with cellular immunity results in injuries that manifest as chronic, symmetric, multi-synovial arthritis and extra-articular lesions.^{137–139} Research to date indicates that irisin can ameliorate joint damage in RA by modulating immune inflammation, necrotic molecules, and biochemical signaling pathways, as well as by inhibiting mitochondrial fission through suppression of the YAP-Drp1 signaling pathway.^{140,141} It has also been proposed that irisin could serve as a novel marker for the early diagnosis of RA-related fractures. Serum irisin level in RA patients was determined by ELISA irisin test system. 37% of patients had lower irisin level, and these patients had higher RA activity and functional joint failure grade.¹⁴² Moreover, levels of serum irisin in female patients with RA have been established to be correlated with osteoporotic vertebral fractures.¹⁴³ Irisin may have a potential role in the diagnosis, treatment, or prognosis of RA, but due to the current scarcity of related data, further in-depth research is required.

Tregs and RA

Whereas inconsistencies have been reported regarding the number of Tregs in the peripheral blood of patients with RA,^{144–149} it is generally found that numbers in the synovial fluid of patients with RA are higher than those in the peripheral blood,^{145,147,150} and that the function of these Tregs is significantly impaired. Moreover, FoxP3-deficient mice had more rapid and aggressive arthritis progression.¹⁵¹ It has been established that Tregs can reduce inflammation, retard synovial tissue damage, and prevent erosive inflammation.¹⁵² For example, Morgan et al have demonstrated that Tregs can effectively alleviate RA symptoms in mice by targeting Tregs using specific monoclonal antibodies followed by the re-infusion of normal Tregs.¹⁵³ Clinical studies have also shown that increasing Tregs number and function can effectively control the progression of RA.^{154,155}

The treatment of RA is mainly based on drug therapy, which can significantly reduce the morbidity and mortality associated with RA, but it is not a cure. Meanwhile, several drugs that affect the number or function of Tregs have been reported to be effective in the treatment of RA. Enhancing the number and function of Tregs may be an effective method for the treatment of RA patients. This makes it possible to improve Tregs function in the treatment of RA as a new and fruitful means.¹⁵⁴

Irisin, Tregs, and RA

It is widely believed that exercise promotes the production of irisin through muscle contraction. However, some studies suggest that exercise may reduce the levels of Tregs in the peripheral blood of elderly RA patients.¹⁵⁶ Furthermore, exercise may also induce chronic arthritis by upregulating local complement activation and inhibiting the Tregs feedback loop.¹⁵⁷ In contrast, other studies provide evidence that exercise can improve related symptoms in RA patients and that different intensities of exercise may have varying effects on the condition of RA patients.^{158,159} Given these contrasting results, whether irisin can improve the prognosis of RA patients by regulating Tregs function still requires further investigation. Despite the differing opinions on whether exercise can improve the condition of RA patients, it is generally believed that irisin is beneficial for RA patients. Firstly, irisin may improve the condition of RA patients by directly reducing synovial inflammation. Additionally, irisin may also reduce synovial inflammation by improving Tregs function, thereby slowing down synovial damage (Figure 7).

In conclusion, although the impact of exercise on RA patients is controversial, irisin may play an important role in the treatment of RA through complex mechanisms of immune system regulation, especially by modulating Tregs function. Further research in this field will help clarify the potential benefits of irisin in RA management.

Discussion

We collected and summarized all current irisin studies on immune-related diseases. irisin was found to treat immune-related diseases mainly through anti-inflammatory effect. Tregs function seems to play an important role in the anti-inflammatory effect of irisin. Especially in the study of exercise improving immune-related diseases, we believe that the myofactor irisin produced by exercise plays a key role in the improvement of patients' condition.

The prevention and treatment of immune-related diseases require the restoration of immune homeostasis, in which Tregs play key roles.¹⁶⁰ To date, only a handful of animal models and clinical studies have provided us with evidence:

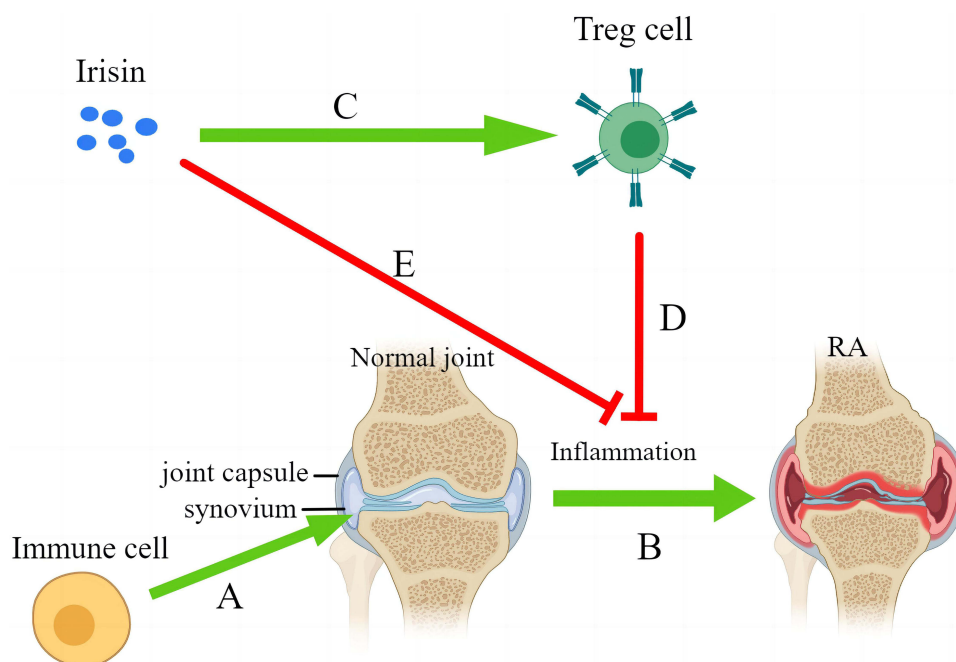


Figure 7 Rheumatoid arthritis (RA) is currently recognised as a chronic systemic autoimmune disease characterised by synovitis. First, immune cells, which attack foreign objects outside the body, gather on the surface of the synovial membrane. They then stimulate the synovium, producing inflammatory substances that cause abnormalities in the synovium and bone (A and B). Irisin may improve RA disease by promoting Tregs function or by directly reducing synovial inflammation (C–E).

moderate physical exercise can significantly increase the number of Tregs and their immunosuppressive function in the blood and tissues, and also maintain the homeostasis of Tregs. Furthermore, exercise enhances the transcriptional activity and epigenetic regulatory capacity of Tregs by upregulating the expression of the transcription factor Foxp3, thereby helping to slow down the progression of immune-related diseases.^{161,162} However, the findings in this field are not always consistent. Such inconsistencies may stem from a variety of factors, including research biases, design flaws, significant variations in the effects of exercise on different individuals, and the high degree of heterogeneity between human and animal studies. Therefore, we cannot yet draw definitive conclusions. Nonetheless, early clinical studies have shed light on the impact of immune-metabolic pathways, particularly during the exercise response process, where the release of catecholamines, the kynurenine pathway, and the cAMP/PPAR β/δ signaling pathway play regulatory roles in modulating the immunosuppressive function of Tregs.^{163,164} Moreover, it has yet to be sufficiently ascertained whether the conditions of individuals with immune-related diseases are improved directly via an altered myokine microenvironment associated with exercise or indirectly via immune system regulation. It is also unclear whether irisin, one of the myokines produced by exercise, is effective in enhancing immune system function and the prognosis of immune-related diseases when acting alone, which warrants further confirmatory research.

In recent years, irisin has been identified as a key myokine; numerous studies have shown that it has anti-inflammatory effects, which require further research to elucidate its role in immune-related diseases. The functional homeostasis of Tregs plays a crucial regulatory role in the progression and remission of immune-related diseases; the regulatory effect of irisin on the functional homeostasis of Tregs and its mechanism remains to be further studied. The role of irisin in regulating Tregs homeostasis in the prevention and treatment of immune-related diseases is not yet fully understood, and related cellular, animal, and clinical studies are relatively few. Existing studies suggest that irisin may improve the immune response in myasthenia gravis (MG) and viral myocarditis by regulating the proportion of Tregs and inhibiting related inflammatory factors.^{55,165} The specific mechanisms may include increasing the proportion of Tregs cells, inhibiting macrophage endoplasmic reticulum stress activation, improving mitochondrial function, and maintaining intracellular redox balance, thereby reducing the secretion of inflammatory factors. Additionally, many studies have confirmed that exercise can improve immune-related diseases by regulating the function of Tregs, with myokines playing an important role in this process, and irisin possibly being one of the key factors. Recent studies have found that integrins

play an important role in regulating Tregs function¹⁶⁶ and can reduce inflammatory responses through the $\alpha\text{V}\beta 5$ pathway.¹² When inflammation occurs, neutrophils can release a net-like structure of DNA and proteins known as NETs through a process called NETosis to capture and kill pathogens. Excessive formation of NETs is associated with various types of inflammation and autoimmune diseases. Tregs can inhibit excessive NETs through anti-inflammatory signals. Research suggests that irisin may significantly reduce the formation of NETs by regulating the P38/MAPK pathway through $\alpha\text{V}\beta 5$ and may improve disease damage by enhancing mitochondrial function.^{109,111,141} In summary, we hypothesize that irisin may promote Tregs function by improving mitochondrial function, reducing Tregs oxidative stress and apoptosis, inducing Tregs differentiation, and releasing anti-inflammatory factors. Furthermore, our current research indicates that irisin can upregulate the expression of $\alpha\text{V}\beta 5$, thereby improving the function of Tregs (data not shown). Additionally, there is an interactive regulatory effect between inflammatory responses and oxidative stress. During inflammation, large amounts of ROS are released, promoting the transcription and expression of various inflammatory signals, forming a vicious cycle. The effect of using anti-inflammatory and antioxidant drugs alone to treat inflammatory diseases is limited and cannot solve the problem fundamentally. Irisin, with its anti-inflammatory and antioxidant properties, may be a candidate drug for treating immune-related diseases. With further understanding of the relationship between irisin, Tregs, and immune-related diseases, we will be able to determine whether the regulation of Tregs functional homeostasis by irisin can provide an effective therapeutic option for immune-related diseases.

Acknowledgments

This work was partially funded by Science and Technology Project of Sichuan Province(NO.2022YFS0632, 2022YFS0627). We would like to thank Editage (www.editage.cn) for English language editing. This paper has been uploaded to Authorea as a preprint: <https://www.authorea.com/users/724943/articles/708516-The-application-potential-of-The-regulation-of-tregs-function-by-irisin-in-The-prevention-and-treatment-of-immune-related-diseases>.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Ferrer-Martinez A, Ruiz-Lozano P, Chien KR. Mouse PeP: a novel peroxisomal protein linked to myoblast differentiation and development. *Dev Dyn*. 2002;224:154–167. doi:10.1002/dvdy.10099
2. Teufel A, Malik N, Mukhopadhyay M, Westphal H. Frp1 and Frp2, two novel fibronectin type III repeat containing genes. *Gene*. 2002;297:79–83. doi:10.1016/S0378-1119(02)00828-4
3. Bostrom P, Wu J, Jedrychowski MP, et al. A PGC1- α -dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature*. 2012;481:463–468. doi:10.1038/nature10777
4. Schumacher MA, Chinnam N, Ohashi T, Shah RS, Erickson HP. The structure of irisin reveals a novel intersubunit β -sheet fibronectin type III (FNIII) dimer: implications for receptor activation. *J Biol Chem*. 2013;288:33738–33744. doi:10.1074/jbc.M113.516641
5. Sun B, Wu H, Lu J, et al. Irisin reduces bone fracture by facilitating osteogenesis and antagonizing TGF- β /Smad signaling in a growing mouse model of osteogenesis imperfecta. *J Orthop Translat*. 2022;38:175–189. doi:10.1016/j.jot.2022.10.012
6. Peng J, Wu J. Effects of the FNDC5/Irisin on Elderly Dementia and Cognitive Impairment. *Front Aging Neurosci*. 2022;14:863901. doi:10.3389/fnagi.2022.863901
7. Zhang QX, Zhang LJ, Zhao N, Chang SH, Yang L. FNDC5/Irisin protects neurons through Caspase 3 and Bax pathways. *Cell Biochem Funct*. 2024;42(1):e3912. doi:10.1002/cbf.3912
8. Li DJ, Li YH, Yuan HB, Qu LF, Wang P. The novel exercise-induced hormone irisin protects against neuronal injury via activation of the Akt and ERK1/2 signaling pathways and contributes to the neuroprotection of physical exercise in cerebral ischemia. *Metabolism*. 2017;68:31–42. doi:10.1016/j.metabol.2016.12.003

9. Trettel CDS, Pelozin BRA, Barros MP, et al. Irisin: an anti-inflammatory exerkine in aging and redox-mediated comorbidities. *Front Endocrinol.* 2023;14:1106529. doi:10.3389/fendo.2023.1106529
10. Zhang X, Xu S, Hu Y, et al. Irisin exhibits neuroprotection by preventing mitochondrial damage in Parkinson's disease. *NPJ Parkinsons Dis.* 2023;9(1):13. doi:10.1038/s41531-023-00453-9
11. Llaverro F, Alejo LB, Fiuza-Luces C, et al. Exercise training effects on natural killer cells: a preliminary proteomics and systems biology approach. *Exerc Immunol Rev.* 2021;27:125–141.
12. Wang Y, Tian M, Tan J, et al. Irisin ameliorates neuroinflammation and neuronal apoptosis through integrin α V β 5/AMPK signaling pathway after intracerebral hemorrhage in mice. *J Neuroinflammation.* 2022;19(1):82. doi:10.1186/s12974-022-02438-6
13. Tu Y, Liu J, Kong D, et al. Irisin drives macrophage anti-inflammatory differentiation via JAK2-STAT6-dependent activation of PPAR γ and Nrf2 signaling. *Free Radic Biol Med.* 2023;201:98–110. doi:10.1016/j.freeradbiomed.2023.03.014
14. Lu J, Xiang G, Liu M, Mei W, Xiang L, Dong J. Irisin protects against endothelial injury and ameliorates atherosclerosis in apolipoprotein E-Null diabetic mice. *Atherosclerosis.* 2015;243(2):438–448. doi:10.1016/j.atherosclerosis.2015.10.020
15. Han F, Ding ZF, Shi XL, et al. Irisin inhibits neutrophil extracellular traps formation and protects against acute pancreatitis in mice. *Redox Biol.* 2023;64:102787. doi:10.1016/j.redox.2023.102787
16. Zhao QY, Shi SJ, Sun DQ, Zhang SS, Zhou XH. [Correlation between galectin-3 level in bronchoalveolar lavage fluid and cellular immunity in children with refractory Mycoplasma pneumoniae pneumonia]. *Zhongguo Dang Dai Er Ke Za Zhi.* 2019;21(2):150–154. Chinese. doi:10.7499/j.issn.1008-8830.2019.02.008
17. Klein L, Robey EA, Hsieh CS. Central CD4+ T cell tolerance: deletion versus regulatory T cell differentiation. *Nat Rev Immunol.* 2019;19(1):7–18. doi:10.1038/s41577-018-0083-6
18. von Knethen A, Heinicke U, Weigert A, Zacharowski K, Brüne B. Histone Deacetylation Inhibitors as Modulators of Regulatory T Cells. *Int J Mol Sci.* 2020;21(7):2356. doi:10.3390/ijms21072356
19. Ramsdell F, Rudensky AY. Foxp3: a genetic foundation for regulatory T cell differentiation and function. *Nat Immunol.* 2020;21(7):708–709. doi:10.1038/s41590-020-0694-5
20. Marcus R. What Is Multiple Sclerosis? *JAMA.* 2022;328(20):2078. doi:10.1001/jama.2022.14236
21. Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. Multiple sclerosis. *Lancet.* 2018;391(10130):1622–1636. doi:10.1016/S0140-6736(18)30481-1
22. Rodríguez Murúa S, Farez MF, Quintana FJ. the immune response in multiple sclerosis. *Annu Rev Pathol.* 2022;17:121–139. doi:10.1146/annurev-pathol-052920-040318
23. Klotz L, Antel J, Kuhlmann T. Inflammation in multiple sclerosis: consequences for remyelination and disease progression. *Nat Rev Neurol.* 2023;19(5):305–320. doi:10.1038/s41582-023-00801-6
24. Malhotra S, Costa C, Eixarch H, et al. NLRP3 inflammasome as prognostic factor and therapeutic target in primary progressive multiple sclerosis patients. *Brain.* 2020;143(5):1414–1430. doi:10.1093/brain/awaa084
25. Musella A, Fresegna D, Rizzo FR, et al. 'Prototypical' proinflammatory cytokine (IL-1) in multiple sclerosis: role in pathogenesis and therapeutic targeting. *Expert Opin Ther Targets.* 2020;24(1):37–46. doi:10.1080/14728222.2020.1709823
26. Khan AW, Farooq M, Hwang MJ, Haseeb M, Choi S. Autoimmune Neuroinflammatory Diseases: role of Interleukins. *Int J Mol Sci.* 2023;24(9):7960. doi:10.3390/ijms24097960
27. Blandford SN, Galloway DA, Williams JB, et al. Interleukin-1 receptor antagonist: an exploratory plasma biomarker that correlates with disability and provides pathophysiological insights in relapsing-remitting multiple sclerosis. *Mult Scler Relat Disord.* 2021;52:103006. doi:10.1016/j.msard.2021.103006
28. Haider L, Zrzavy T, Hametner S, et al. The topography of demyelination and neurodegeneration in the multiple sclerosis brain. *Brain.* 2016;139(Pt 3):807–815. doi:10.1093/brain/awv398
29. Haider L, Fischer MT, Frischer JM, et al. Oxidative damage in multiple sclerosis lesions. *Brain.* 2011;134(Pt 7):1914–1924. doi:10.1093/brain/awr128
30. Bizoń A, Chojdak-lukasiewicz J, Budrewicz S, Pokryszko-Dragan A, Piwowar A. Exploring the relationship between antioxidant enzymes, oxidative stress markers, and clinical profile in relapsing-remitting multiple sclerosis. *Antioxidants.* 2023;12(8):1638. doi:10.3390/antiox12081638
31. Zhang QX, Zhang SN, Zhang LJ, Zhang DQ, Yang L. Irisin levels in the serum and cerebrospinal fluid of patients with multiple sclerosis and the expression and distribution of irisin in experimental autoimmune encephalomyelitis. *Clin Exp Immunol.* 2021;206(2):208–215. doi:10.1111/cei.13656
32. Bilek F, Cetisli-Korkmaz N, Ercan Z, Deniz G, Demir CF. Aerobic exercise increases irisin serum levels and improves depression and fatigue in patients with relapsing remitting multiple sclerosis: a randomized controlled trial. *Mult Scler Relat Disord.* 2022;61:103742. doi:10.1016/j.msard.2022.103742
33. Briken S, Rosenkranz SC, Keminer O, et al. Effects of exercise on Irisin, BDNF and IL-6 serum levels in patients with progressive multiple sclerosis. *J Neuroimmunol.* 2016;299:53–58. doi:10.1016/j.jneuroim.2016.08.007
34. Altas M, Uca AU, Akdag T, Odabas FO, Tokgoz OS. Serum levels of irisin and nesfatin-1 in multiple sclerosis. *Arq Neuropsiquiatr.* 2022;80(2):161–167. doi:10.1590/0004-282X-ANP-2020-0520
35. Algul S, Ozcelik O. Evaluating the energy regulatory hormones of nesfatin-1, irisin, adropin and preptin in multiple sclerosis. *Mult Scler Relat Disord.* 2022;68:104221. doi:10.1016/j.msard.2022.104221
36. Souza PS, Gonçalves ED, Pedroso GS, et al. Physical exercise attenuates experimental autoimmune encephalomyelitis by inhibiting peripheral immune response and blood-brain barrier disruption. *Mol Neurobiol.* 2017;54(6):4723–4737. doi:10.1007/s12035-016-0014-0
37. Ben-Nun A, Kaushansky N, Kawakami N, et al. From classic to spontaneous and humanized models of multiple sclerosis: impact on understanding pathogenesis and drug development. *J Autoimmun.* 2014;54:33–50. doi:10.1016/j.jaut.2014.06.004
38. Zohar Y, Wildbaum G, Novak R, et al. CXCL11-dependent induction of FOXP3-negative regulatory T cells suppresses autoimmune encephalomyelitis. *J Clin Invest.* 2014;124(5):2009–2022. doi:10.1172/JCI71951
39. Goverman JM. Regulatory T Cells in Multiple Sclerosis. *N Engl J Med.* 2021;384(6):578–580. doi:10.1056/NEJMcibr2033544
40. Chou WC, Guo Z, Guo H, et al. AIM2 in regulatory T cells restrains autoimmune diseases. *Nature.* 2021;591(7849):300–305. doi:10.1038/s41586-021-03231-w

41. Malviya M, Saoudi A, Bauer J, Fillatreau S, Liblau R. Treatment of experimental autoimmune encephalomyelitis with engineered bi-specific Foxp3+ regulatory CD4+ T cells. *J Autoimmun.* 2020;108:102401. doi:10.1016/j.jaut.2020.102401
42. Chwojnicky K, Iwaszkiewicz-Grześ D, Jankowska A, et al. Administration of CD4+CD25highCD127-FoxP3+ regulatory t cells for relapsing-remitting multiple sclerosis: a phase 1 study. *BioDrugs.* 2021;35(1):47–60. doi:10.1007/s40259-020-00462-7
43. Ferraro D, De Biasi S, Simone AM, et al. Modulation of Tregs and iNKT by fingolimod in multiple sclerosis patients. *Cells.* 2021;10(12):3324. doi:10.3390/cells10123324
44. Duffy SS, Keating BA, Perera CJ, et al. Regulatory T cells and their derived cytokine, interleukin-35, reduce pain in experimental autoimmune encephalomyelitis. *J Neurosci.* 2019;39(12):2326–2346. doi:10.1523/JNEUROSCI.1815-18.2019
45. Howard JF. Myasthenia gravis: the role of complement at the neuromuscular junction. *Ann NY Acad Sci.* 2018;1412(1):113–128. doi:10.1111/nyas.13522
46. Huda R. Inflammation and autoimmune myasthenia gravis. *Front Immunol.* 2023;14:1110499. doi:10.3389/fimmu.2023.1110499
47. Morren JA, Li Y. Myasthenia gravis: frequently asked questions. *Cleve Clin J Med.* 2023;90(2):103–113. doi:10.3949/ccjm.90a
48. Gilhus NE. Myasthenia Gravis. *N Engl J Med.* 2016;375(26):2570–2581. doi:10.1056/NEJMra1602678
49. Uzawa A, Kawaguchi N, Himuro K, Kanai T, Kuwabara S. Serum cytokine and chemokine profiles in patients with myasthenia gravis. *Clin Exp Immunol.* 2014;176(2):232–237. doi:10.1111/cei.12272
50. Uzawa A, Kawaguchi N, Kanai T, Himuro K, Oda F, Kuwabara S. Increased serum peroxiredoxin 5 levels in myasthenia gravis. *J Neuroimmunol.* 2015;287:16–18. doi:10.1016/j.jneuroim.2015.07.013
51. Uzawa A, Kawaguchi N, Kanai T, Himuro K, Kuwabara S. Serum high mobility group box 1 is upregulated in myasthenia gravis. *J Neurol Neurosurg Psychiatry.* 2015;86(6):695–697. doi:10.1136/jnnp-2014-309232
52. Molin CJ, Westerberg E, Punga AR. Profile of upregulated inflammatory proteins in sera of Myasthenia Gravis patients. *Sci Rep.* 2017;7:39716. doi:10.1038/srep39716
53. Zhang SN, Li Q, Zhang QX, et al. Serum irisin levels in patients with myasthenia gravis. *Neurol Sci.* 2022;43(4):2785–2790. doi:10.1007/s10072-021-05652-x
54. Yan-Chun MOU, Ya-ting ZHAO, Zhan-Shuai Z. Predictive value of serum Irisin, IL-1 β and TNF- α in crisis of patients with myasthenia gravis. *J Brain Neurolog Dis.* 2019;32(01):22–25.
55. Li GE. *A preliminary Study on the Role and Mechanism of Irisin in Myasthenia Gravis.* Hainan medical college; 2021; doi:10.27952/d.cnki.gghnyx.2021.000003
56. Danikowski KM, Jayaraman S, Prabhakar BS. Regulatory T cells in multiple sclerosis and myasthenia gravis. *J Neuroinflammation.* 2017;14(1):117. doi:10.1186/s12974-017-0892-8
57. Wang N, Yuan J, Karim MR, et al. Effects of mitophagy on regulatory T cell function in patients with myasthenia gravis. *Front Neurol.* 2020;11:238. doi:10.3389/fneur.2020.00238
58. Thiruppathi M, Rowin J, Ganesh B, et al. Impaired regulatory function in circulating CD4(+)CD25(high)CD127(low/-) T cells in patients with myasthenia gravis. *Clin Immunol.* 2012;145(3):209–223. doi:10.1016/j.clim.2012.09.012
59. Ha JC, Richman DP. Myasthenia gravis and related disorders: pathology and molecular pathogenesis. *Biochim Biophys Acta.* 2015;1852(4):651–657. doi:10.1016/j.bbdis.2014.11.022
60. Uzawa A, Kuwabara S, Suzuki S, et al. Roles of cytokines and T cells in the pathogenesis of myasthenia gravis. *Clin Exp Immunol.* 2021;203(3):366–374. doi:10.1111/cei.13546
61. Renton AE, Pliner HA, Provenzano C, et al. A genome-wide association study of myasthenia gravis. *JAMA Neurol.* 2015;72(4):396–404. doi:10.1001/jamaneurol.2014.4103
62. Masuda M, Matsumoto M, Tanaka S, et al. Clinical implication of peripheral CD4+CD25+ regulatory T cells and Th17 cells in myasthenia gravis patients. *J Neuroimmunol.* 2010;225(1–2):123–131. doi:10.1016/j.jneuroim.2010.03.016
63. Sun Y, Qiao J, Lu CZ, et al. Increase of circulating CD4+CD25+ T cells in myasthenia gravis patients with stability and thymectomy. *Clin Immunol.* 2004;112(3):284–289. doi:10.1016/j.clim.2004.04.005
64. Aricha R, Reuveni D, Fuchs S, Souroujon MC. Suppression of experimental autoimmune myasthenia gravis by autologous T regulatory cells. *J Autoimmun.* 2016;67:57–64. doi:10.1016/j.jaut.2015.09.005
65. Sheng JR, Muthusamy T, Prabhakar BS, Meriggioli MN. GM-CSF-induced regulatory T cells selectively inhibit anti-acetylcholine receptor-specific immune responses in experimental myasthenia gravis. *J Neuroimmunol.* 2011;240–241:65–73. doi:10.1016/j.jneuroim.2011.10.010
66. Sauter D, Kirchhoff F. Key viral adaptations preceding the AIDS pandemic. *Cell Host Microbe.* 2019;25(1):27–38. PMID: 30629915. doi:10.1016/j.chom.2018.12.002
67. Srinivasa S, Wong K, Fitch KV, et al. Effects of lifestyle modification and metformin on irisin and FGF21 among HIV-infected subjects with the metabolic syndrome. *Clin Endocrinol.* 2015;82(5):678–685. doi:10.1111/cen.12582
68. Trombeta JCS, Prestes J, Nascimento DC, et al. New insights into the effects of irisin levels in HIV-infected subjects: correlation with adiposity, fat-free mass, and strength parameters[J]. *Arch Endocrinol Metab.* 2017;61:382–390. doi:10.1590/2359-3997000000270
69. Kazer SW, Walker BD, Shalek AK. Evolution and diversity of immune responses during acute HIV infection. *Immunity.* 2020;53(5):908–924. doi:10.1016/j.immuni.2020.10.015
70. Tuano KS, Seth N, Chinen J. Secondary immunodeficiencies: an overview. *Ann Allergy Asthma Immunol.* 2021;127(6):617–626. doi:10.1016/j.anai.2021.08.413
71. Xiang Y, Zhang M, Jiang D, Su Q, Shi J. The role of inflammation in autoimmune disease: a therapeutic target. *Front Immunol.* 2023;14:1267091. doi:10.3389/fimmu.2023.1267091
72. Pisetsky DS. Pathogenesis of autoimmune disease. *Nat Rev Nephrol.* 2023;19(8):509–524. doi:10.1038/s41581-023-00720-1
73. Hunt PW. HIV and inflammation: mechanisms and consequences. *Curr HIV/AIDS Rep.* 2012;9(2):139–147. doi:10.1007/s11904-012-0118-8
74. Schulze Zur Wiesch J, Thomssen A, Hartjen P, et al. Comprehensive analysis of frequency and phenotype of T regulatory cells in HIV infection: CD39 expression of FoxP3+ T regulatory cells correlates with progressive disease. *J Virol.* 2011;85(3):1287–1297. doi:10.1128/JVI.01758-10
75. Yero A, Shi T, Farnos O, et al. Dynamics and epigenetic signature of regulatory T-cells following antiretroviral therapy initiation in acute HIV infection. *EBioMedicine.* 2021;71:103570. doi:10.1016/j.ebiom.2021.103570

76. Yero A, Farnos O, Rabezanahary H, Racine G, Estaquier J, Jenabian MA. Differential dynamics of regulatory T-Cell and Th17 cell balance in mesenteric lymph nodes and blood following early antiretroviral initiation during acute simian immunodeficiency virus infection. *J Virol.* 2019;93(19):e00371–19. doi:10.1128/JVI.00371-19
77. Suchard MS, Mayne E, Green VA, et al. FOXP3 expression is upregulated in CD4T cells in progressive HIV-1 infection and is a marker of disease severity. *PLoS One.* 2010;5(7):e11762. doi:10.1371/journal.pone.0011762
78. Estes JD, Li Q, Reynolds MR, et al. Premature induction of an immunosuppressive regulatory T cell response during acute simian immunodeficiency virus infection. *J Infect Dis.* 2006;193(5):703–712. doi:10.1086/500368
79. Chevalier MF, Weiss L. The split personality of regulatory T cells in HIV infection. *Blood.* 2013;121(1):29–37. doi:10.1182/blood-2012-07-409755
80. Kleinman AJ, Sivanandham R, Pandrea I, Choungnet CA, Apreti C. Regulatory T Cells As Potential Targets for HIV Cure Research. *Front Immunol.* 2018;9:734. doi:10.3389/fimmu.2018.00734
81. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. *Lancet.* 2018;391(10138):2449–2462. doi:10.1016/S0140-6736(18)31320-5
82. Bluestone JA, Buckner JH, Herold KC. Immunotherapy: building a bridge to a cure for type 1 diabetes. *Science.* 2021;373(6554):510–516. doi:10.1126/science.abh1654
83. Donath MY, Dinarello CA, Mandrup-Poulsen T. Targeting innate immune mediators in type 1 and type 2 diabetes. *Nat Rev Immunol.* 2019;19(12):734–746. doi:10.1038/s41577-019-0213-9
84. Verhulst CEM, van Heck JIP, Fabricius TW, et al. Hypo-RESOLVE consortium. Hypoglycaemia induces a sustained pro-inflammatory response in people with type 1 diabetes and healthy controls. *Diabetes Obes Metab.* 2023;25(11):3114–3124. doi:10.1111/dom.15205
85. Canet F, Diaz-Pozo P, Luna-Marco C, et al. Mitochondrial redox impairment and enhanced autophagy in peripheral blood mononuclear cells from type 1 diabetic patients. *Redox Biol.* 2022;58:102551. doi:10.1016/j.redox.2022.102551
86. Bathina S, Das UN. Resolvin D1 decreases severity of streptozotocin-induced type 1 diabetes mellitus by enhancing BDNF levels, reducing oxidative stress, and suppressing inflammation. *Int J Mol Sci.* 2021;22(4):1516. doi:10.3390/ijms22041516
87. Eftekharpour E, Fernyhough P. Oxidative stress and mitochondrial dysfunction associated with peripheral neuropathy in type 1 diabetes. *Antioxid Redox Signal.* 2022;37(7–9):578–596. PMID: 34416846. doi:10.1089/ars.2021.0152
88. Ates I, Arikian MF, Erdogan K, et al. Factors associated with increased irisin levels in the type 1 diabetes mellitus. *Endocr Regul.* 2017;51(1):1–7. doi:10.1515/enr-2017-0001
89. Espes D, Lau J, Carlsson PO. Increased levels of irisin in people with long-standing Type 1 diabetes. *Diabet Med.* 2015;32(9):1172–1176. doi:10.1111/dme.12731
90. Faienza MF, Brunetti G, Sanesi L, et al. High irisin levels are associated with better glycemic control and bone health in children with Type 1 diabetes. *Diabet Res Clin Pract.* 2018;141:10–17. doi:10.1016/j.diabres.2018.03.046
91. Melling CW, Gris  KN, Hasilo CP, et al. A model of poorly controlled type 1 Diabetes Mellitus and its treatment with aerobic exercise training. *Diabetes Metab.* 2013;39(3):226–235. doi:10.1016/j.diabet.2013.02.004
92. Natalicchio A, Marrano N, Biondi G, et al. the myokine irisin is released in response to saturated fatty acids and promotes pancreatic β -cell survival and insulin secretion. *Diabetes.* 2017;66(11):2849–2856. doi:10.2337/db17-0002
93. Cabello-Kindelan C, Mackey S, Sands A, et al. Immunomodulation followed by antigen-specific treg infusion controls islet autoimmunity. *Diabetes.* 2020;69(2):215–227. doi:10.2337/db19-0061
94. Hope CM, Welch J, Mohandas A, et al. Peptidase inhibitor 16 identifies a human regulatory T-cell subset with reduced FOXP3 expression over the first year of recent onset type 1 diabetes. *Eur J Immunol.* 2019;49(8):1235–1250. doi:10.1002/eji.201948094
95. Ovcinnikovs V, Walker LS. Regulatory T cells in autoimmune diabetes: mechanisms of action and translational potential. *Prog Mol Biol Transl Sci.* 2015;136:245–277. doi:10.1016/bs.pmbts.2015.08.004
96. Zhang J, Chen L, Wang F, et al. Extracellular HMGB1 exacerbates autoimmune progression and recurrence of type 1 diabetes by impairing regulatory T cell stability. *Diabetologia.* 2020;63(5):987–1001. doi:10.1007/s00125-020-05105-8
97. Viisanen T, Gazali AM, Ihtantola EL, et al. FOXP3+ regulatory T cell compartment is altered in children with newly diagnosed type 1 diabetes but not in autoantibody-positive at-risk children. *Front Immunol.* 2019;10:19. doi:10.3389/fimmu.2019.00019
98. Yamauchi T, Takasawa K, Kamiya T, et al. Hematopoietic stem cell transplantation recovers insulin deficiency in type 1 diabetes mellitus associated with IPEX syndrome. *Pediatr Diabetes.* 2019;20(7):1035–1040. doi:10.1111/pedi.12895
99. Ben-Skowronek I, Sieniawska J, Pach E, et al. Potential therapeutic application of regulatory T cells in diabetes mellitus type 1. *Int J Mol Sci.* 2021;23(1):390. doi:10.3390/ijms23010390
100. Yu H, Paiva R, Flavell RA. Harnessing the power of regulatory T-cells to control autoimmune diabetes: overview and perspective. *Immunology.* 2018;153(2):161–170. doi:10.1111/imm.12867
101. Singer M, Deutschman CS, Seymour CW, et al. The Third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA.* 2016;315(8):801–810. doi:10.1001/jama.2016.0287
102. Brealey D, Karyampudi S, Jacques TS, et al. Mitochondrial dysfunction in a long-term rodent model of sepsis and organ failure. *Am J Physiol Regul Integr Comp Physiol.* 2004;286(3):R491–7. doi:10.1152/ajpregu.00432.2003
103. Levy RJ, Vijayasarathy C, Raj NR, Avadhani NG, Deutschman CS. Competitive and noncompetitive inhibition of myocardial cytochrome C oxidase in sepsis. *Shock.* 2004;21(2):110–114. doi:10.1097/01.shk.0000108400.56565.ab
104. Hotchkiss RS, Swanson PE, Freeman BD, et al. Apoptotic cell death in patients with sepsis, shock, and multiple organ dysfunction. *Crit Care Med.* 1999;27(7):1230–1251. doi:10.1097/00003246-199907000-00002
105. Heidecke CD, Hensler T, Weighardt H, et al. Selective defects of T lymphocyte function in patients with lethal intraabdominal infection. *Am J Surg.* 1999;178(4):288–292. doi:10.1016/s0002-9610(99)00183-x
106. Limaye AP, Kirby KA, Rubenfeld GD, et al. Cytomegalovirus reactivation in critically ill immunocompetent patients. *JAMA.* 2008;300(4):413–422. doi:10.1001/jama.300.4.413
107. Li Q, Zhang M, Zhao Y, Dong M. Irisin protects against LPS-stressed cardiac damage through inhibiting inflammation, apoptosis, and pyroptosis. *Shock.* 2021;56(6):1009–1018. doi:10.1097/SHK.0000000000001775
108. Jiang X, Cai S, Jin Y, et al. Irisin attenuates oxidative stress, mitochondrial dysfunction, and apoptosis in the H9C2 cellular model of septic cardiomyopathy through augmenting fundc1-dependent mitophagy. *Oxid Med Cell Longev.* 2021;2021:2989974. doi:10.1155/2021/2989974

109. Xiong X, Lu L, Wang Z, et al. Irisin attenuates sepsis-induced cardiac dysfunction by attenuating inflammation-induced pyroptosis through a mitochondrial ubiquitin ligase-dependent mechanism. *Biomed Pharmacother.* 2022;152:113199. doi:10.1016/j.biopha.2022.113199
110. Ouyang H, Li Q, Zhong J, et al. Combination of melatonin and irisin ameliorates lipopolysaccharide-induced cardiac dysfunction through suppressing the Mst1-JNK pathways. *J Cell Physiol.* 2020;235(10):6647–6659. doi:10.1002/jcp.29561
111. Tan Y, Ouyang H, Xiao X, Zhong J, Dong M. Irisin ameliorates septic cardiomyopathy via inhibiting DRP1-related mitochondrial fission and normalizing the JNK-LATS2 signaling pathway. *Cell Stress Chaperones.* 2019;24(3):595–608. doi:10.1007/s12192-019-00992-2
112. Wang J, Zhu Q, Wang Y, Peng J, Shao L, Li X. Irisin protects against sepsis-associated encephalopathy by suppressing ferroptosis via activation of the Nrf2/GPX4 signal axis. *Free Radic Biol Med.* 2022;187:171–184. doi:10.1016/j.freeradbiomed.2022.05.023
113. Qiongyue Z, Xin Y, Meng P, et al. Post-treatment with irisin attenuates acute kidney injury in sepsis mice through anti-ferroptosis via the SIRT1/Nrf2 Pathway. *Front Pharmacol.* 2022;13:857067. doi:10.3389/fphar.2022.857067
114. Li X, Jamal M, Guo P, et al. Irisin alleviates pulmonary epithelial barrier dysfunction in sepsis-induced acute lung injury via activation of AMPK/SIRT1 pathways. *Biomed Pharmacother.* 2019;118:109363. doi:10.1016/j.biopha.2019.109363
115. Li Q, Tan Y, Chen S, et al. Irisin alleviates LPS-induced liver injury and inflammation through inhibition of NLRP3 inflammasome and NF- κ B signaling. *J Recept Signal Transduction Res.* 2021;41(3):294–303. doi:10.1080/10799893.2020.1808675
116. Jin YH, Li ZY, Jiang XQ, et al. Irisin alleviates renal injury caused by sepsis via the NF- κ B signaling pathway. *Eur Rev Med Pharmacol Sci.* 2020;24(11):6470–6476. doi:10.26355/eurev_202006_21546
117. Wei S, Bi J, Yang L, et al. Serum irisin levels are decreased in patients with sepsis, and exogenous irisin suppresses ferroptosis in the liver of septic mice. *Clin Transl Med.* 2020;10(5):e173. doi:10.1002/ctm2.173
118. Williams PT. Inadequate exercise as a risk factor for sepsis mortality. *PLoS One.* 2013;8(12):e79344. doi:10.1371/journal.pone.0079344
119. de Araújo CC, Silva JD, Samary CS, et al. Regular and moderate exercise before experimental sepsis reduces the risk of lung and distal organ injury. *J Appl Physiol.* 2012;112(7):1206–1214. doi:10.1152/jappphysiol.01061.2011
120. Sossdorf M, Fischer J, Meyer S, et al. Physical exercise induces specific adaptations resulting in reduced organ injury and mortality during severe polymicrobial sepsis. *Crit Care Med.* 2013;41(10):e246–55. doi:10.1097/CCM.0b013e31828a2ae3
121. Olivo CR, Miyaji EN, Oliveira ML, et al. Aerobic exercise attenuates pulmonary inflammation induced by Streptococcus pneumoniae. *J Appl Physiol.* 2014;117(9):998–1007. doi:10.1152/jappphysiol.00290.2014
122. Tyml K, Swarbreck S, Pape C, et al. Voluntary running exercise protects against sepsis-induced early inflammatory and pro-coagulant responses in aged mice. *Crit Care.* 2017;21(1):210. PMID: 28789683; PMCID: PMC5549433. doi:10.1186/s13054-017-1783-1
123. Pedersen BK, Febbraio MA. Muscle as an endocrine organ: focus on muscle-derived interleukin-6. *Physiol Rev.* 2008;88(4):1379–1406. doi:10.1152/physrev.90100.2007
124. Raschke S, Eckel J. Adipo-myokines: two sides of the same coin--mediators of inflammation and mediators of exercise. *Mediators Inflamm.* 2013;2013:320724. doi:10.1155/2013/320724
125. Venet F, Pachot A, Debard AL, et al. Increased percentage of CD4+CD25+ regulatory T cells during septic shock is due to the decrease of CD4+CD25- lymphocytes. *Crit Care Med.* 2004;32(11):2329–2331. doi:10.1097/01.ccm.0000145999.42971.4b
126. Heuer JG, Zhang T, Zhao J, et al. Adoptive transfer of in vitro-stimulated CD4+CD25+ regulatory T cells increases bacterial clearance and improves survival in polymicrobial sepsis. *J Immunol.* 2005;174(11):7141–7146. doi:10.4049/jimmunol.174.11.7141
127. Scumpia PO, Delano MJ, Kelly KM, et al. Increased natural CD4+CD25+ regulatory T cells and their suppressor activity do not contribute to mortality in murine polymicrobial sepsis. *J Immunol.* 2006;177(11):7943–7949. doi:10.4049/jimmunol.177.11.7943
128. Wisnoski N, Chung CS, Chen Y, Huang X, Ayala A. The contribution of CD4+ CD25+ T-regulatory-cells to immune suppression in sepsis. *Shock.* 2007;27(3):251–257. doi:10.1097/01.shk.0000239780.33398.e4
129. Chen X, Bäuml M, Männel DN, Howard OM, Oppenheim JJ. Interaction of TNF with TNF receptor type 2 promotes expansion and function of mouse CD4+CD25+ T regulatory cells. *J Immunol.* 2007;179(1):154–161. doi:10.4049/jimmunol.179.1.154
130. Xie J, Wang H, Kang Y, et al. Chinese epidemiological study of sepsis (CHESS) study investigators. the epidemiology of sepsis in Chinese icus: a national cross-sectional survey. *Crit Care Med.* 2020;48(3):e209–e218. doi:10.1097/CCM.0000000000004155
131. Weng L, Zeng XY, Yin P, et al.; China Critical Care Clinical Trials Group (CCCCTG). Sepsis-related mortality in China: a descriptive analysis. *Intensive Care Med.* 2018;44(7):1071–1080. doi:10.1007/s00134-018-5203-z
132. Markwart R, Saito H, Harder T, et al. Epidemiology and burden of sepsis acquired in hospitals and intensive care units: a systematic review and meta-analysis. *Intensive Care Med.* 2020;46(8):1536–1551. doi:10.1007/s00134-020-06106-2
133. Gao YL, Yao Y, Zhang X, et al. Regulatory T Cells: angels or demons in the pathophysiology of sepsis? *Front Immunol.* 2022;13:829210. doi:10.3389/fimmu.2022.829210
134. Taylor AL, Llewelyn MJ. Superantigen-induced proliferation of human CD4+CD25- T cells is followed by a switch to a functional regulatory phenotype. *J Immunol.* 2010;185(11):6591–6598. PMID: 21048104.126. doi:10.4049/jimmunol.1002416
135. Nascimento DC, Alves-Filho JC, Sonego F, et al. Role of regulatory T cells in long-term immune dysfunction associated with severe sepsis. *Crit Care Med.* 2010;38(8):1718–1725. doi:10.1097/CCM.0b013e3181e78ad0
136. Martin MD, Badovinac VP, Griffith TS. CD4 T Cell Responses and the Sepsis-Induced Immunoparalysis State. *Front Immunol.* 2020;11:1364. doi:10.3389/fimmu.2020.01364
137. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet.* 2016;388(10055):2023–2038. doi:10.1016/S0140-6736(16)30173-8
138. Smith MH, Berman JR. What Is Rheumatoid Arthritis? *JAMA.* 2022;327(12):1194. doi:10.1001/jama.2022.0786
139. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *N Engl J Med.* 2011;365(23):2205–2219. doi:10.1056/NEJMra1004965
140. Raafat Ibrahim R, Shafik NM, El-Esawy RO, et al. The emerging role of irisin in experimentally induced arthritis: a recent update involving HMGB1/MCP1/Chitotriosidase I-mediated necroptosis. *Redox Rep.* 2022;27(1):21–31. doi:10.1080/13510002.2022.2031516
141. Yu Y, Ma M, Li C, et al. Irisin mitigates rheumatoid arthritis by suppressing mitochondrial fission via inhibiting YAP-Drp1 signaling pathway. *Int Immunopharmacol.* 2024;127:111443. doi:10.1016/j.intimp.2023.111443
142. Lavrova DP, Zavodovsky BV, Akhverdyan YR, et al. [Irisin as a new marker for the early diagnosis of low-traumatic fractures in rheumatoid arthritis]. *Klin Lab Diagn.* 2018;63(11):702–706. Russian. doi:10.18821/0869-2084-2018-63-11-702-706
143. Gamez-Nava JI, Ramirez-Villafañá M, Cons-Molina F, et al. Serum irisin concentrations and osteoporotic vertebral fractures in women with rheumatoid arthritis: a cross-sectional study. *Medicine.* 2022;101(6):e28799. doi:10.1097/MD.00000000000028799

144. Niu Q, Cai B, Huang ZC, Shi YY, Wang LL. Disturbed Th17/Treg balance in patients with rheumatoid arthritis. *Rheumatol Int.* 2012;32(9):2731–2736. doi:10.1007/s00296-011-1984-x
145. Cao D, Malmström V, Baecher-Allan C, et al. Isolation and functional characterization of regulatory CD25 bright CD4 + T cells from the target organ of patients with rheumatoid arthritis. *Eur J Immunol.* 2003;33(1):215–223. doi:10.1002/immu.200390024
146. Han GM, O'Neil-Andersen NJ, Zurier RB, Lawrence DA. CD4+CD25high T cell numbers are enriched in the peripheral blood of patients with rheumatoid arthritis. *Cell Immunol.* 2008;253(1–2):92–101. doi:10.1016/j.cellimm.2008.05.007
147. van Amelsfort JM, Jacobs KM, Bijlsma JW, Lafèber FP, Taams LS. CD4(+)CD25(+) regulatory T cells in rheumatoid arthritis: differences in the presence, phenotype, and function between peripheral blood and synovial fluid. *Arthritis Rheum.* 2004;50(9):2775–2785. doi:10.1002/art.20499
148. Cao D, van Vollenhoven R, Klareskog L, Trollmo C, Malmström V. CD25brightCD4+ regulatory T cells are enriched in inflamed joints of patients with chronic rheumatic disease. *Arthritis Res Ther.* 2004;6(4):R335–46. doi:10.1186/ar1192
149. Ehrenstein MR, Evans JG, Singh A, et al. Compromised function of regulatory T cells in rheumatoid arthritis and reversal by anti-TNFalpha therapy. *J Exp Med.* 2004;200(3):277–285. doi:10.1084/jem.20040165
150. Möttönen M, Heikkinen J, Mustonen L, et al. CD4+ CD25+ T cells with the phenotypic and functional characteristics of regulatory T cells are enriched in the synovial fluid of patients with rheumatoid arthritis. *Clin Exp Immunol.* 2005;140(2):360–367. doi:10.1111/j.1365-2249.2005.02754.x
151. Nie H, Zheng Y, Li R, et al. Phosphorylation of FOXP3 controls regulatory T cell function and is inhibited by TNF-α in rheumatoid arthritis. *Nat Med.* 2013;19(3):322–328. doi:10.1038/nm.3085
152. Leipe J, Skapenko A, Lipsky PE, Schulze-Koops H. Regulatory T cells in rheumatoid arthritis. *Arthritis Res Ther.* 2005;7(3):93. doi:10.1186/ar1718
153. Morgan ME, Suttmuller RP, Witteveen HJ, et al. CD25+ cell depletion hastens the onset of severe disease in collagen-induced arthritis. *Arthritis Rheum.* 2003;48(5):1452–1460. doi:10.1002/art.11063
154. Esensten JH, Wofsy D, Bluestone JA. Regulatory T cells as therapeutic targets in rheumatoid arthritis. *Nat Rev Rheumatol.* 2009;5(10):560–565. doi:10.1038/nrrheum.2009.183
155. Jiang Q, Yang G, Liu Q, Wang S, Cui D. Function and Role of Regulatory T Cells in Rheumatoid Arthritis. *Front Immunol.* 2021;12:626193. doi:10.3389/fimmu.2021.626193
156. Andersson SEM, Lange E, Kucharski D, et al. Moderate- to high intensity aerobic and resistance exercise reduces peripheral blood regulatory cell populations in older adults with rheumatoid arthritis. *Immun Ageing.* 2020;17:12. doi:10.1186/s12979-020-00184-y
157. Cambré I, Gaublumme D, Schryvers N, et al. Running promotes chronicity of arthritis by local modulation of complement activators and impairing T regulatory feedback loops. *Ann Rheum Dis.* 2019;78(6):787–795. doi:10.1136/annrheumdis-2018-214627
158. Lamb SE, Williamson EM, Heine PJ, et al. Strengthening and Stretching for Rheumatoid Arthritis of the Hand Trial (SARAH) Trial Team. Exercises to improve function of the rheumatoid hand (SARAH): a randomised controlled trial. *Lancet.* 2015;385(9966):421–429. doi:10.1016/S0140-6736(14)60998-3
159. Østerås N, Kjekken I. A tailored hand exercise program improves function of the rheumatoid hand. *J Physiother.* 2015;61(2):96. doi:10.1016/j.jphys.2015.02.007
160. Lamb SE, Williamson EM, Heine PJ, et al. Exercises to improve function of the rheumatoid hand (SARAH): a randomised controlled trial. *Lancet.* 2015;385(9966):421–429. doi:10.1016/S0140-6736(14)60998-3
161. Weinhold M, Shimabukuro-Vornhagen A, Franke A, et al. Physical exercise modulates the homeostasis of human regulatory T cells. *J Allergy Clin Immunol.* 2016;137(5):1607–1610.e8. doi:10.1016/j.jaci.2015.10.035
162. Lowder T, Dugger K, Deshane J, Estell K, Schwiebert LM. Repeated bouts of aerobic exercise enhance regulatory T cell responses in a murine asthma model. *Brain Behav Immun.* 2010;24(1):153–159. doi:10.1016/j.bbi.2009.09.011
163. Proschinger S, Winker M, Joisten N, et al. The effect of exercise on regulatory T cells: a systematic review of human and animal studies with future perspectives and methodological recommendations. *Exerc Immunol Rev.* 2021;27:142–166.
164. Dorneles GP, Dos Passos AAZ, Romão PRT, Peres A. New insights about regulatory t cells distribution and function with exercise: the role of immunometabolism. *Curr Pharm Des.* 2020;26(9):979–990. doi:10.2174/1381612826666200305125210
165. Fangjuan W, Xuejiao L, Julong H. Iris pigment irisin immunoregulatory effects of viral myocarditis mice. *J Immunol.* 2021;5(8):652–658.
166. Sun H, Lagarrigue F, Wang H, et al. Distinct integrin activation pathways for effector and regulatory T cell trafficking and function. *J Exp Med.* 2021;218(2):e20201524. doi:10.1084/jem.20201524

Drug Design, Development and Therapy

Dovepress

Publish your work in this journal

Drug Design, Development and Therapy is an international, peer-reviewed open-access journal that spans the spectrum of drug design and development through to clinical applications. Clinical outcomes, patient safety, and programs for the development and effective, safe, and sustained use of medicines are a feature of the journal, which has also been accepted for indexing on PubMed Central. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/drug-design-development-and-therapy-journal>