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REVIEW

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

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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

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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-1β, 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 irisine 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

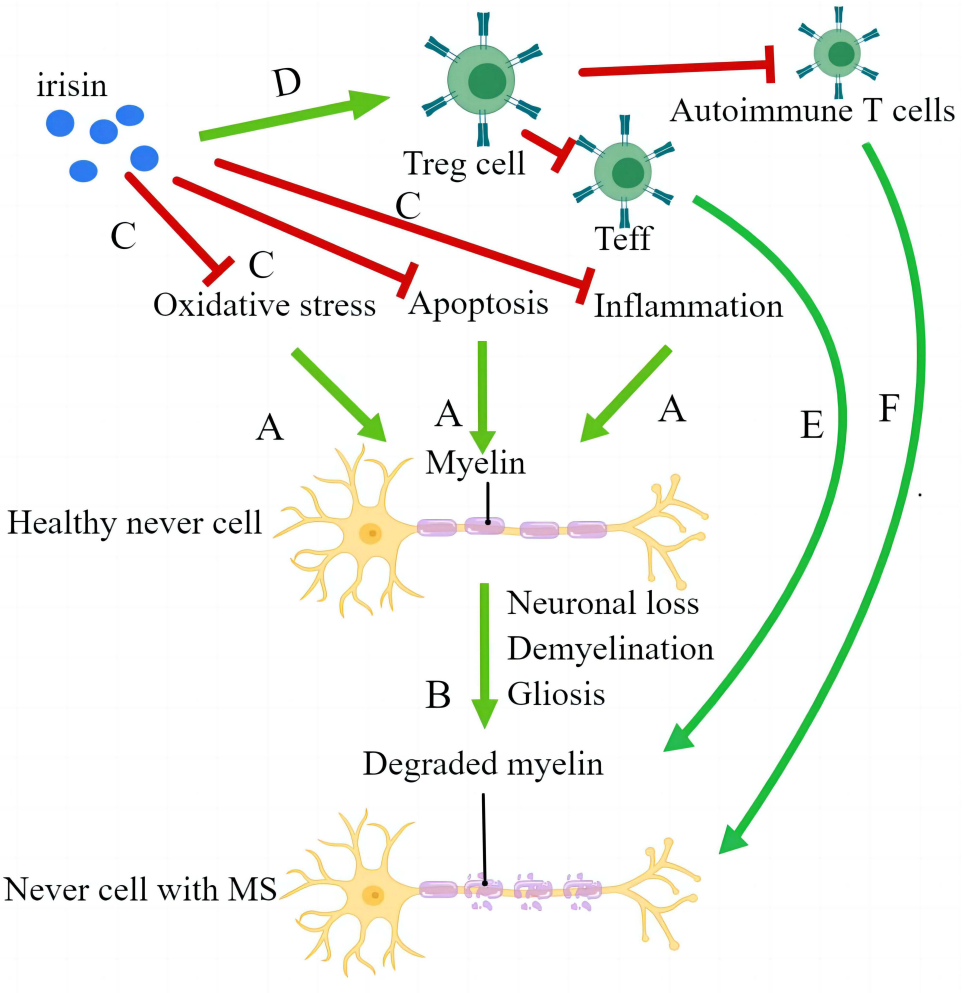

Figure 1 Multiple sclerosis (MS) presents with multifocal demyelination of the central nervous system (A and B). Irisin improves MS by improving demyelination caused by inflammation, oxidative stress, and apoptosis, as well as reducing neuronal loss and glial cell formation caused by axonal injury (C). At the same time, irisin may treat MS by improving Tregs function (D) and inhibiting myelin destruction caused by Teff (efferent 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 al[64] and Sheng et al[65] 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 effects[55] (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 immunog). 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;

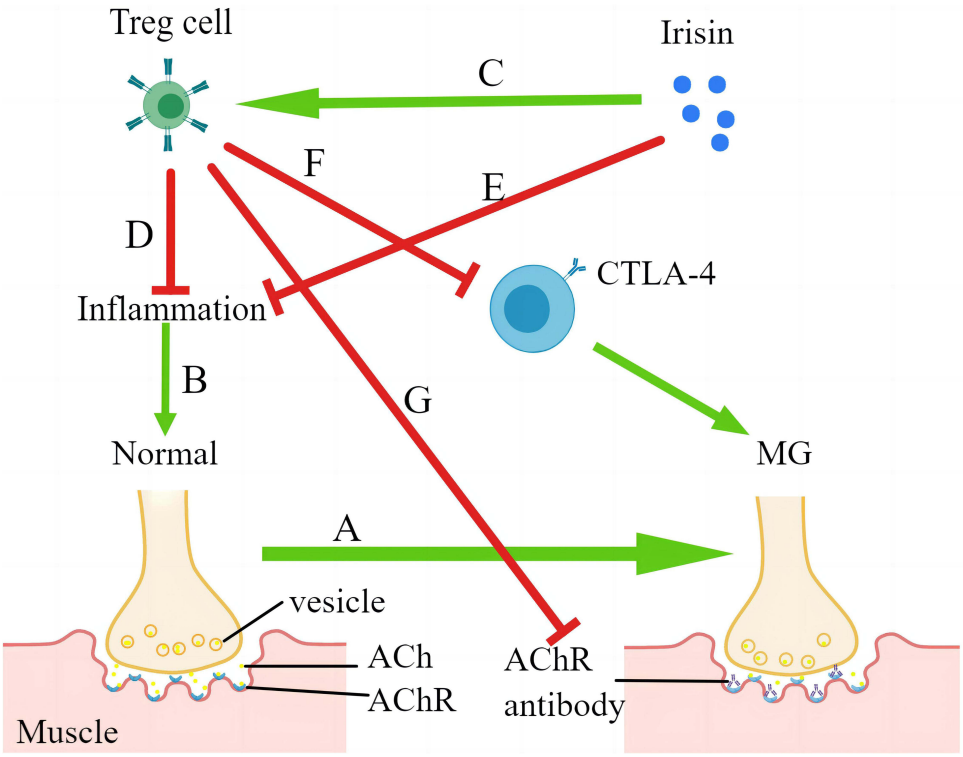

Figure 2 Myasthenia gravis (MG) is an immune-related disease in which autoantibodies attack the skeletal muscle acetylcholine receptor (AChR), resulting in neuromuscular junction transmission disorders (A). Inflammatory mediators and cytokines are closely related to the development of MG (B). Irisin 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, Trombeta 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-cells[81] (Figure 4). It is an inflammatory disease[82,83] that is mainly characterised by an intense inflammatory response that

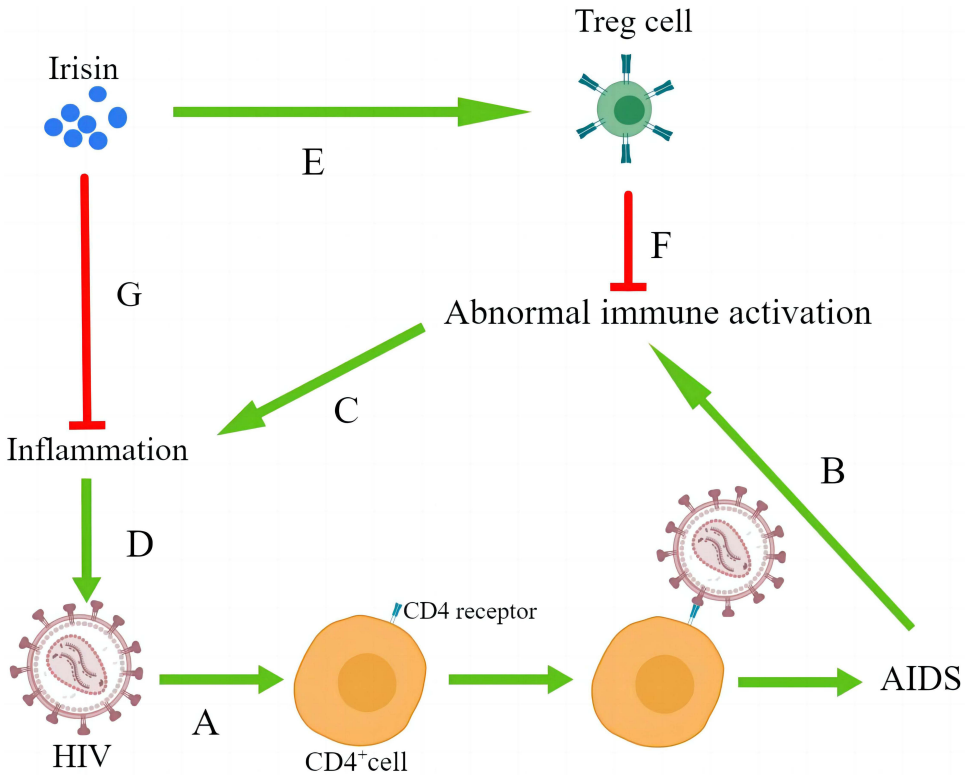

Figure 3 Acquired Immune Deficiency Syndrome (AIDS) refers to immunodeficiency caused by human immunodeficiency virus (HIV) infection (A). The major changes in the immune system of patients with AIDS include a reduced number and dysfunction of $CD4^+$ T lymphocytes, abnormal immune activation (B), and 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 dose[89] 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.

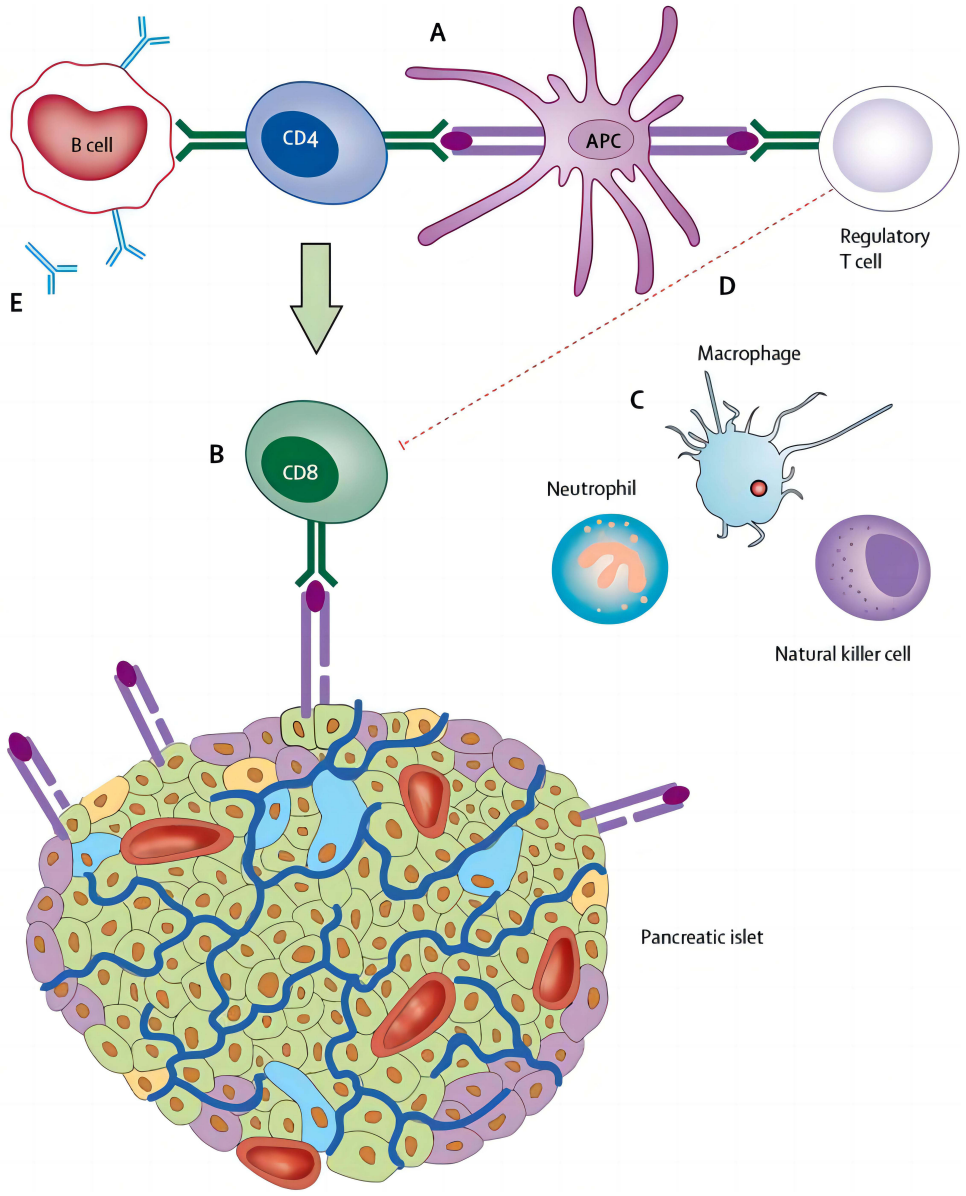

Figure 4 The development of type 1 diabetes is thought to be initiated by the presentation of β-cell peptides by antigen-presenting cells (APCs). APCs bearing these autoantigens migrate to the pancreatic lymph nodes, where they interact with autoreactive $CD4^+$ T lymphocytes, which in turn mediate the 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 Jun16;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-10Rα), TGF-β1, and TGF-β2, 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.

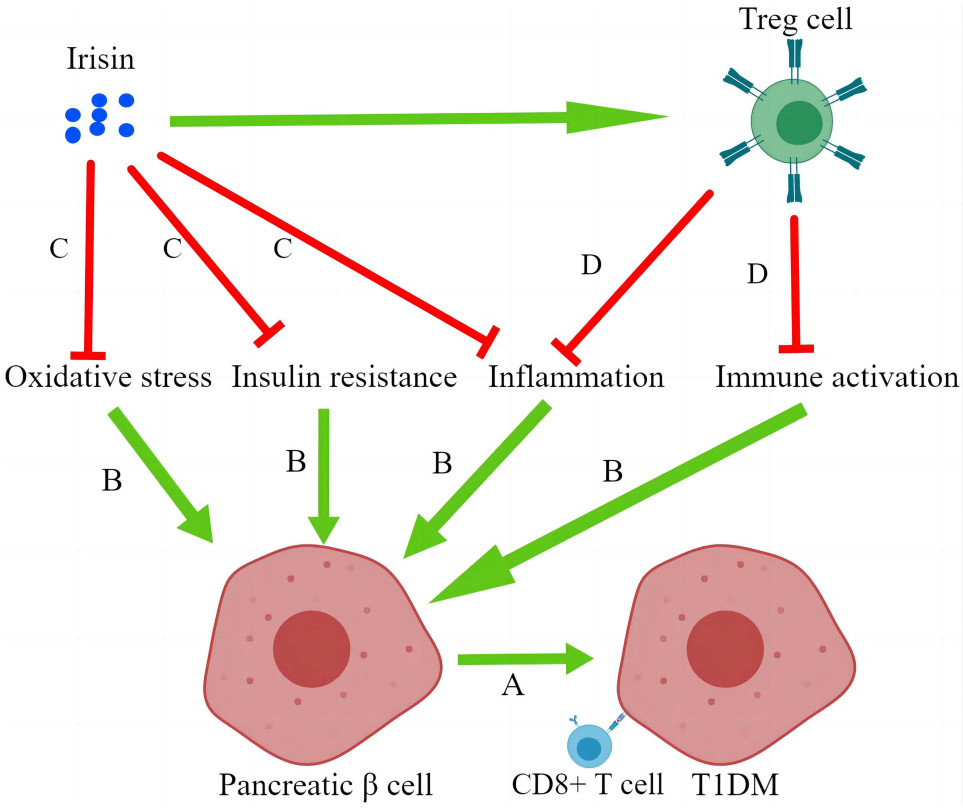

Figure 5 Activated $CD8^+$ T cells attack islet β-cells, resulting in type 1 diabetes mellitus (T1DM) (A). Oxidative stress, insulin resistance, inflammation, and immune activation may promote this process (B). Irisin treats T1DM by improving oxidative stress and insulin resistance (C) and promoting 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) pathway[110] 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)-κB 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-κB 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

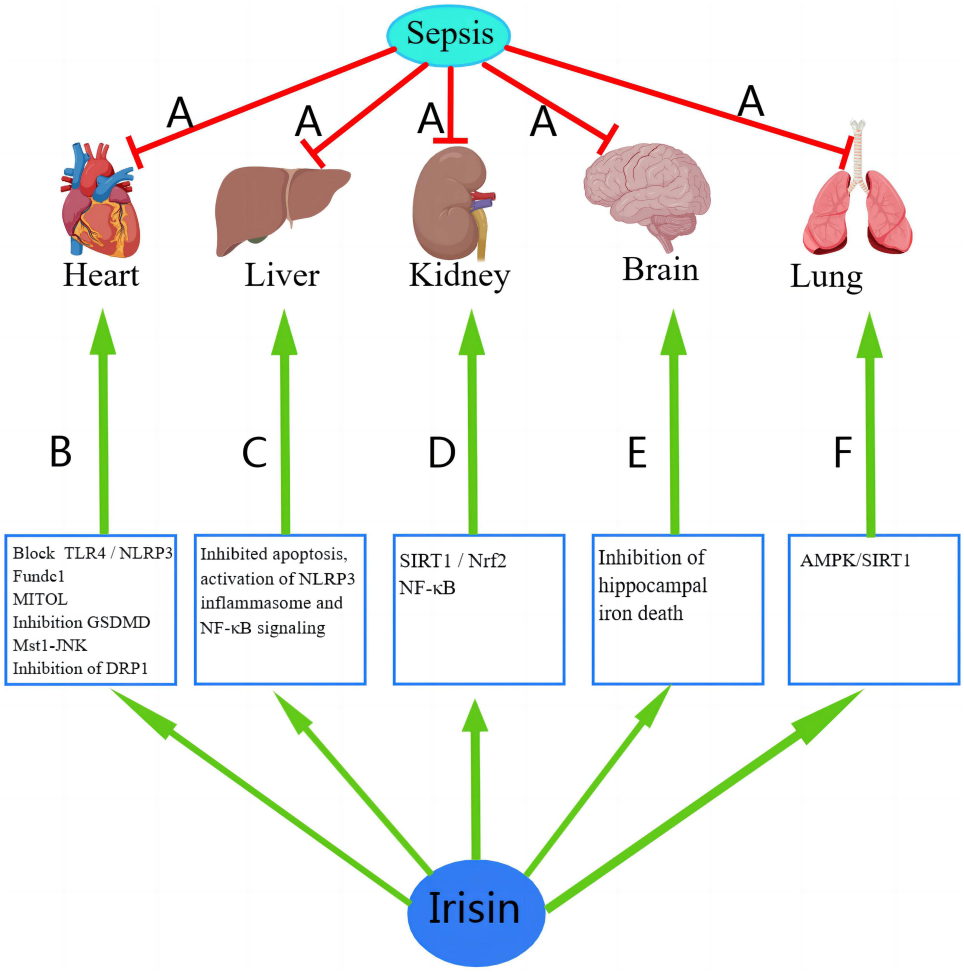

Figure 6 Sepsis can cause multiple organ dysfunctions (A). Irisin can improve sepsis-related cardiac dysfunction in various ways, including by blocking the TLR4/NLRP3 signalling pathway to inhibit inflammation, apoptosis, and pyrodeath and through FundC1-related mitochondrial autophagy. It alleviates 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:

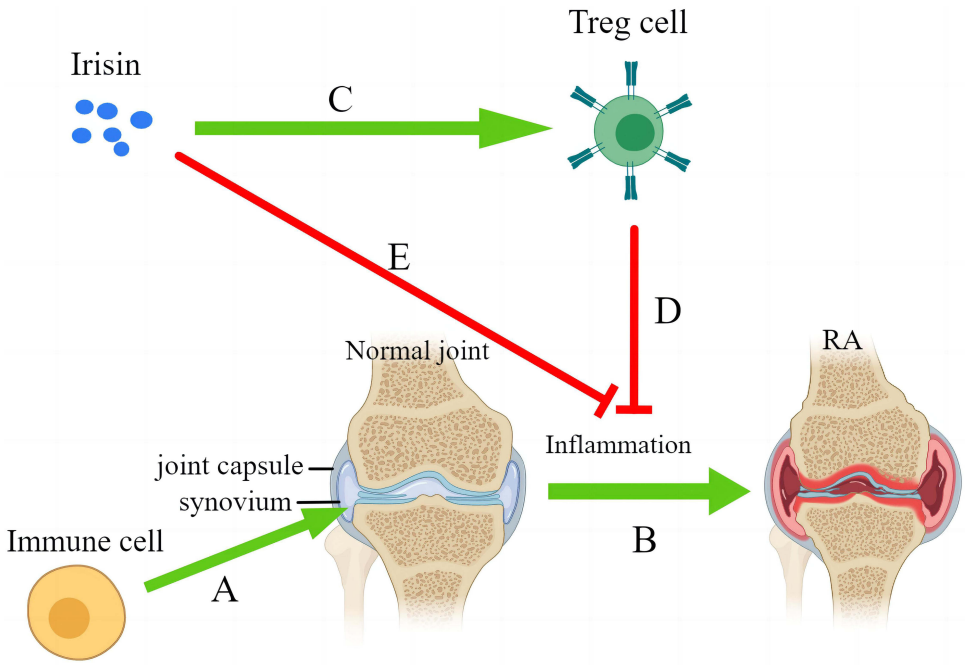

Figure 7 Rheumatoid arthritis (RA) is currently recognised as a chronic systemic autoimmune disease characterised by synovitis. First, immune cells, which attack foreign objects outside the body, gather on the surface of the synovial membrane. They then stimulate the synovium, producing inflammatory 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/PPARβ/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 function[166] and can reduce inflammatory responses through the αvβ5 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 αVβ5 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 αvβ5, 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.

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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.

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