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REVIEW

Mechanisms and Drug-Augmenting Strategies of Mesenchymal Stem Cells for Preserving β-Cell in Type 2 Diabetes

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Abstract: Type 2 diabetes (T2D) is closely linked to β-cell dysfunction. Preserving β-cell function has emerged as a critical therapeutic strategy for T2D. Mesenchymal stem cells (MSCs) have demonstrated remarkable potential in achieving this goal. This paper systematically reviews the multifaceted mechanisms by which MSCs protect pancreatic β-cell function in T2D. It integrates eight core mechanisms: modulating the inflammatory microenvironment, regulating the immune system, counteracting oxidative stress, enhancing autophagy levels, alleviating endoplasmic reticulum stress, safeguarding mitochondrial function, promoting β-cell regeneration and repair, and inhibiting ferroptosis. Together, these form a multi-layered, networked intervention system. This framework elucidates MSC protective effects across three functional levels: eliminating injury initiators, maintaining cellular homeostasis, and intervening in cellular fate outcomes. Additionally, this review examines pharmacological strategies to enhance MSC efficacy, including hypoglycemic agents, other drugs, and natural products, with a focus on their mechanisms of action and barriers to clinical translation. Finally, based on MSC advantages and existing research limitations, we propose future research directions, including optimizing MSC source selection and engineering MSC-derived exosomes. These recommendations aim to provide theoretical foundations and strategic references for MSC-based T2D therapies.

Keywords: mesenchymal stem cells, type 2 diabetes, β-cell, hypoglycemic agents, natural products

Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia, which has become one of the most prevalent chronic diseases globally. In 2024, the global prevalence of diabetes among adults reached 11.11%, with the number of people living with diabetes surpassing 500 million that year. It is projected to approach 900 million by 2050.[1] Currently, type 2 diabetes (T2D) constitutes the predominant form of DM. Data indicate that T2D accounts for 96.0% of all DM cases.[2]

Recent studies have shown that β-cell dysfunction is central to the onset and progression of T2D. Although insulin resistance is one of the hallmark features of the disease, it is ultimately the insufficient secretion of insulin by β-cells that drives the development of hyperglycemia.[3] Further research indicates that persistent β-cell dysfunction, rather than a loss of β-cell mass, is a key factor in the early development of T2D.[4] Hyperinsulinemia, insulin resistance, β-cell dysfunction, and hyperglycemia all mark the transition from health to T2D. The relative importance and sequence of these

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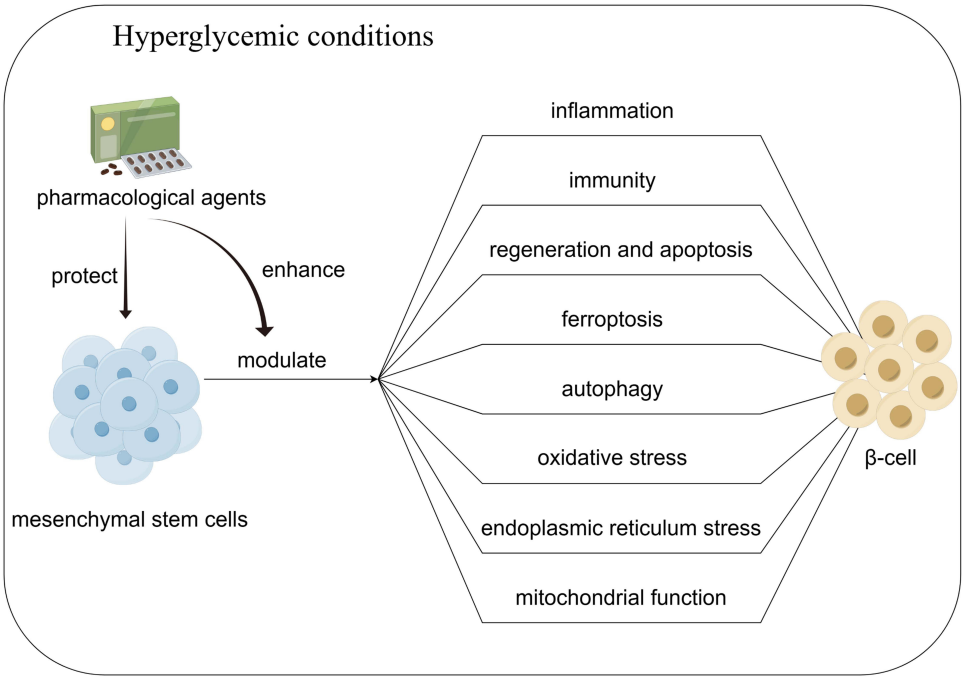
Graphical Abstract



pathological changes are currently a matter of debate and may vary from person to person; however, the prevailing view remains that β-cell dysfunction leading to chronic hyperglycemia constitutes the pathogenesis of T2D.[5,6]

Metabolic abnormalities are a key driver of β-cell dysfunction. Glucotoxicity or lipotoxicity induced by hyperglycemia or excessive free fatty acids activates multiple damage pathways, including inflammation, oxidative stress, endoplasmic reticulum stress, and mitochondrial damage, leading to β-cell dysfunction, apoptosis, or dedifferentiation, and ultimately resulting in insufficient insulin secretion. This is currently the mainstream mechanism underlying β-cell damage.[7,8] Furthermore, the unique characteristics of pancreatic islet tissue and insulin-such as the low antioxidant enzyme activity in islet tissue and the complex tertiary structure of proinsulin-are also significant factors contributing to the susceptibility of β-cells to damage.[9,10] (Figure 1)

Persistent hyperglycemia leads to excessive oxidative damage, endothelial dysfunction, and chronic inflammation through pathways such as the polyol pathway, the formation of advanced glycation end products (AGEs), the activation of protein kinase C, as well as oxidative stress. It also reduces protective compounds such as nitric oxide and prostacyclin, ultimately resulting in macrovascular and microvascular complications.[11–13] Hyperglycemia-induced damage to cellular tissues also creates a "metabolic memory", driven by reactive oxygen species (ROS), AGEs, and persistent inflammation, which continues to promote the development of complications even after blood glucose levels are controlled.[11]

Mesenchymal stem cells (MSCs) are mesoderm-derived, multipotent adult stem cells with capabilities for self-renewal and multilineage differentiation. They circumvent the ethical concerns associated with embryonic stem cells (ESCs) and avoid the tumorigenic risks linked to induced pluripotent stem cells (iPSCs), making MSCs ideal candidates for both immunomodulatory and regenerative applications.[14] Owing to their homing capacity, multilineage differentiation potential, secretion of numerous bioactive factors, and potent immunomodulatory functions, MSCs have emerged as a promising therapeutic strategy for various diseases in both basic research and clinical trials.[15,16]

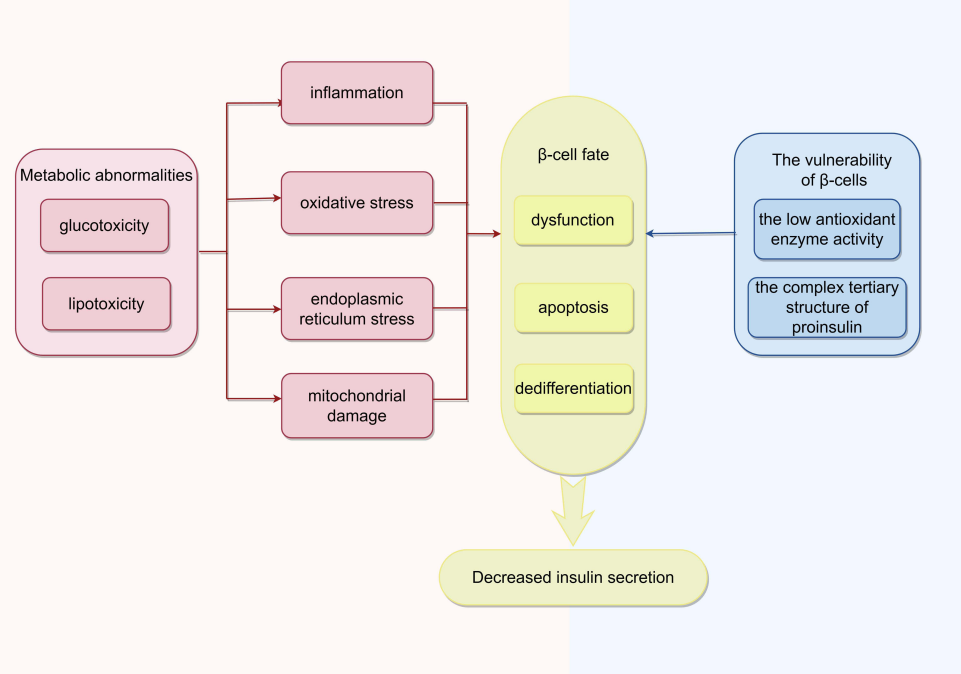


Figure 1 Drivers of β-cell damage: Metabolic abnormalities and pancreatic tissue vulnerability drive β-cell damage, with external metabolic abnormalities currently being the primary focus of research.

MSCs exert protective effects on β-cell function primarily through potent paracrine signaling,[17–19] the release of extracellular vesicles (EVs),[20–24] and other mechanisms, and these actions can reverse β-cell dedifferentiation[25,26] and repair damaged β-cells, thereby restoring functional islet mass. Consequently, MSCs represent a highly promising therapeutic approach for T2D. Among the various tissue sources, adipose-derived MSCs (AD-MSCs), umbilical cord-derived MSCs (UC-MSCs), and bone marrow-derived MSCs (BM-MSCs) are among the most extensively studied and clinically applied. All three MSC types have demonstrated efficacy in improving β-cell function in animal models of T2D.[17,27,28]

Clinical trials have demonstrated the advantages of combining hypoglycemic agents with MSCs for the treatment of T2D.[29] Consequently, beyond their synergistic glucose-lowering effects, a critical question emerges: whether and how these hypoglycemic agents can act upon MSCs to augment their protective effects on β-cells through multifaceted efficacy-enhancing mechanisms. Elucidating this issue is essential for guiding precise clinical drug application. Furthermore, in recent years, natural products (NPs) have garnered increasing attention due to their exceptional chemical diversity and structural complexity, high bioactivity and specificity, multi-target mechanisms of action, favorable safety profiles, and increasingly standardized quality control.[30,31] Studies have confirmed that NPs can protect MSCs from damage in hyperglycemic environments, thereby enhancing their functionality.[32] Additionally, NPs can preserve or promote MSC function through various pathways,[33,34] indicating their significant potential in supporting MSCs to exert their normal therapeutic effects.

Although studies have indicated that MSCs can preserve or restore β-cell function in individuals with T2D, the underlying mechanisms involved are numerous and intricately interconnected. Delineating these mechanisms is crucial for the further development of MSC-based therapies. Moreover, few studies have specifically designed drug intervention experiments targeting MSC function within the context of β-cell injury or hyperglycemic microenvironments, indicating a need for greater research precision in this area. In this review, we aim to provide a comprehensive overview of MSCs as a promising therapy for T2D, with particular emphasis on their β-cell protective mechanisms and strategies to enhance their efficacy through pharmacological interventions.

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Research Type and Methodology

This article is a narrative review of the literature on the mechanisms by which mesenchymal stem cells (MSCs) protect pancreatic β-cell function in type 2 diabetes (T2D) and the pharmacological strategies to enhance MSC efficacy. A comprehensive literature search was conducted using the following electronic databases: PubMed, PubScholar.The following keywords and their combinations were used: "mesenchymal stem cells," "MSCs," "type 2 diabetes," "T2D," "β-cell," "islet," "inflammation," "immune regulation," "oxidative stress," "autophagy," "endoplasmic reticulum stress," "mitochondrial transfer," "ferroptosis," "apoptosis," "regeneration," "hypoglycemic agents," "metformin," "GLP-1," "natural products," and "drug augmentation."

Mechanisms of Mesenchymal Stem Cells in Preserving β-Cell Function

We have summarized eight areas that are currently well-researched and at the forefront of the field, including: modulation of the inflammatory microenvironment, regulation of the immune system, promotion of β-cell regeneration and apoptosis resistance, inhibition of ferroptosis, enhancement of autophagy, attenuation of oxidative stress, alleviation of endoplasmic reticulum stress and preservation of mitochondrial function.(Figure 2)

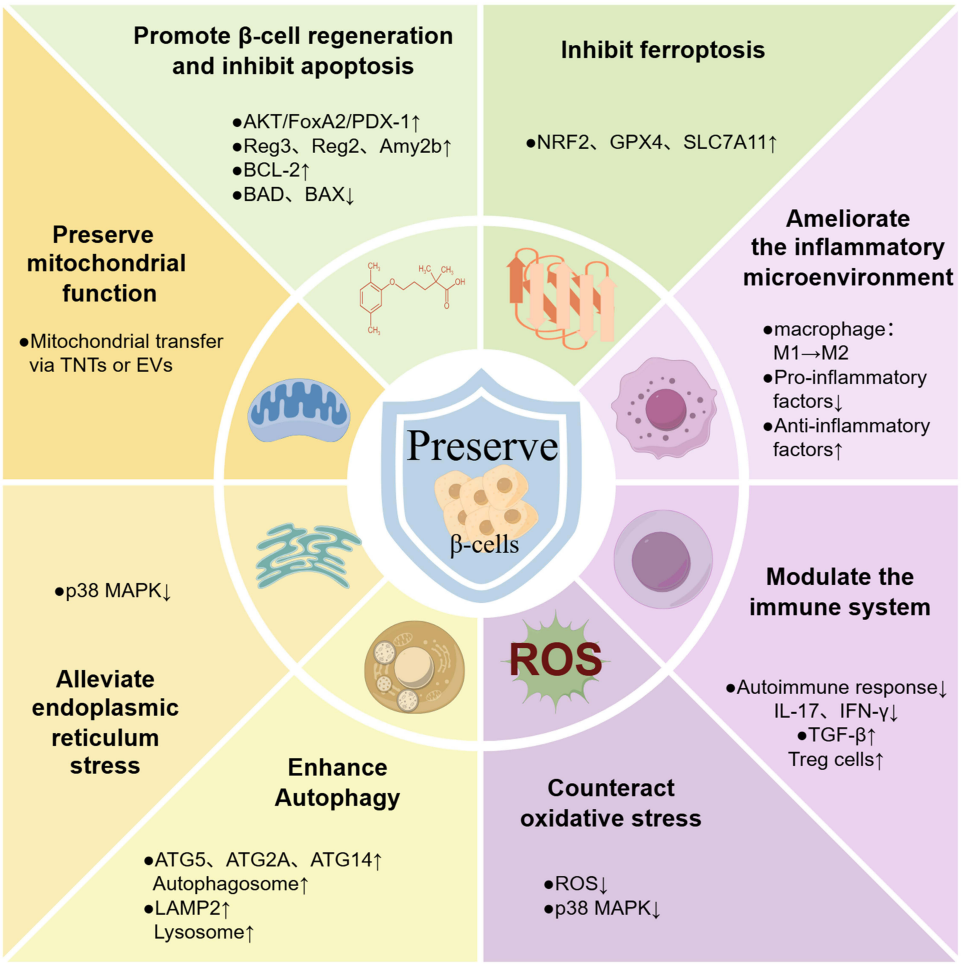

Figure 2 How MSCs Preserve β-Cell Function: An Overview: This figure illustrates the eight mechanisms by which MSCs preserve β-cell function: Amelioration of the inflammatory microenvironment; Modulation of the immune system; Counteraction of oxidative stress; Enhancement of autophagic activity; Alleviation of endoplasmic reticulum stress; Preservation of mitochondrial function; Promotion of β-cell regeneration and inhibition of apoptosis; Inhibition of ferroptosis. In this figure, the upward arrow "↑" is used to represent promotion or increase, and the downward arrow "↓" represents inhibition or decrease.

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Eliminating the Drivers of β-Cells Damage

Preservation of β-Cells from Inflammatory Microenvironment Damage

Inflammation is a key mechanism underlying β-cell dysfunction in T2D. Characteristically, the islets of T2D patients exhibit a significant increase in pro-inflammatory cytokines[35] and macrophage numbers,[36,37] accompanied by suppressed expression of proinsulin mRNA.[38] This is because during the progression of T2D, M1 macrophages accumulate within the islets,[39] and the pro-inflammatory cytokines they secrete impair the function of β-cells.[40,41] Thus, M1 macrophages and associated pro-inflammatory mediators are major contributors to β-cell dysfunction within the inflammatory microenvironment.

UC-MSCs can suppress M1 macrophage activation and induce the conversion of macrophages to the anti-inflammatory M2 phenotype by secreting monocyte chemoattractant protein-1 (MCP-1) and interleukin-6 (IL-6).[17,42] Exosomes derived from AD-MSCs (AD-MSC-Exos) can be internalized by macrophages, significantly increasing the mRNA levels of arginase-1 (Arg-1) and interleukin-10 (IL-10), indicating that AD-MSC-Exos also induce macrophage polarization to the M2 phenotype.[43] Beyond mitigating inflammation, M2 macrophages can directly enhance β-cell proliferation and functional recovery by upregulating SMAD family member 7 (SMAD7).[44]

β-cell dedifferentiation is a primary mechanism involved in T2D, contributing to a greater extent than apoptosis.[25] MSCs can reverse β-cell dedifferentiation through an IL-1 receptor antagonist (IL-1Ra)-mediated pathway. MSCs respond to elevated pro-inflammatory cytokine expression in human T2D islets. Interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α), highly expressed in T2D islets, activate MSCs to secrete IL-1Ra. This acts on inflamed islets to prevent excessive inflammatory responses and reverse β-cell dedifferentiation.[26]

MSCs can also broadly modulate the inflammatory cytokine network, thereby mitigating inflammatory damage to β-cells. Experimental results indicate that following MSC infusion therapy, expression of pro-inflammatory cytokines such as IL-6, interleukin-17 (IL-17), IL-1β, and TNF-α was significantly reduced, while expression of anti-inflammatory cytokines like IL-10 and adiponectin was markedly elevated. Ultimately, β-cell proliferation and survival rates were significantly increased.[45–48] Additionally, BM-MSCs can partially rescue IL-1β/interferon-γ (IFN-γ)-induced functional impairment in INS-1 cells.[49]

In summary, the mechanism by which MSCs protect pancreatic β-cells through modulating the inflammatory microenvironment is as follows: (1) Inducing M1 macrophages to transition to the anti-inflammatory M2 phenotype can both alleviate inflammation and directly promote β-cell proliferation and functional recovery. (2) Responding to highly expressed pro-inflammatory cytokines by secreting IL-1Ra, thus preventing excessive inflammation and reversing β-cell dedifferentiation in an IL-1Ra-mediated manner. (3) Broadly modulate inflammatory cytokine levels to reduce pro-inflammatory cytokine expression and increase anti-inflammatory cytokine expression, thereby alleviating inflammation-induced damage to β-cells and restoring their normal proliferation and function.

Regulation of the Immune System

Immune dysregulation is a hallmark in some T2D patients and is intricately linked to the development of inflammation, both processes can promote the onset and progression of T2D.[50,51] Specific pathological markers include: the presence of autoantibodies against glutamic acid decarboxylase (GAD) (a typical pancreatic islet cell autoantigen in type 1 diabetes mellitus (T1D));[52–55] and the defects of autoreactive T cells or regulatory T cells (Tregs).[56] Research indicates that the severe impairment of insulin secretion observed in islet autoantibody-positive T2D patients is closely related to immune-mediated β-cell damage.[57]

MSCs and/or MSC-Exos demonstrate immunosuppressive properties by increasing the population of Tregs and their associated products. Following treatment, elevated levels of interleukin-4 (IL-4), IL-10, and transforming growth factor-beta (TGF-β) can be detected, alongside reduced levels of IL-17 and IFN-γ.[58–61] Among these, TGF-β promotes the differentiation of naïve T cells into Tregs and is critical for maintaining peripheral immune tolerance. In contrast, overexpression of IFN-γ and IL-17 is a pathogenic factor in autoimmune diseases; notably, IFN-γ can upregulate the expression of MHC class I and II molecules on antigen-presenting cells, serving as a key driver of immune activation.

MSCs or their derived microvesicles (MVs) can modulate immune responses against GAD antigens, reducing levels of IFN-γ and IL-17 stimulated by GAD65 while increasing levels of TGF-β, PGE2, and IL-10. This was accompanied by

a decrease in T helper 17 cells (Th17) and an increase in Forkhead box P3 (Foxp3)+ Tregs.[62,63] PGE2 can upregulate the Treg-specific marker Foxp3, contributing to immunosuppression.[64]

Additionally, plasmablasts can act as antigen-presenting cells that promote CD4+ T cell activation and contribute to T cell-mediated β-cell destruction. Patients receiving MSC transplants have been observed to exhibit reduced plasmablast counts and preserved β-cell function.[65]

In summary, the key to the immunomodulatory effects of MSCs lies in Treg cells, which play a crucial role in maintaining immune tolerance and suppressing immune responses against GAD antigens. Additionally, MSCs can reduce the number of Th17 cells and plasmablasts, thereby inhibiting autoimmune reactions. Although most of the above mechanisms have currently only been validated in T1D, the presence of immune dysregulation—such as Treg deficiency—in T2D suggests that immunomodulatory therapies targeting these pathways may also hold promise for T2D treatment.

Counteraction of Oxidative Stress

A persistent hyperglycemic environment enhances glycolysis and pyruvate production in β-cells. Due to the low expression of lactate dehydrogenase (LDH) and monocarboxylate transporter 1 (MCT-1) in β-cells, pyruvate cannot be metabolized via the lactate pathway. Instead, it is almost entirely oxidized through mitochondrial oxidative phosphorylation, leading to increased generation of ROS.[66,67] ROS activates mitogen-activated protein kinases (MAPKs), such as c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (p38 MAPK). This activation enhances the degradation of key β-cell transcription factors, including pancreatic and duodenal homeobox 1 (PDX-1) and V-maf musculoaponeurotic fibrosarcoma oncogene homolog A (MAFA), thereby reducing insulin gene expression.[68] Additionally, JNK, activated by ROS, induces cell apoptosis by modulating the expression of genes critical for cell proliferation and survival, such as B-cell lymphoma-extra large (BCL-XL) and B-cell lymphoma 2 (BCL-2).[69,70] More importantly,the activity of major antioxidant enzymes in pancreatic tissue is relatively low.[10] Therefore, the ability of MSCs to counteract oxidative stress is of paramount importance for preserving β-cell function.

MSCs prevent oxidative stress from damaging β-cells through three pathways:First, they directly inhibit ROS production. This includes upregulating lysosome-associated membrane protein 2 (LAMP2) expression to enhance autophagosome and lysosome formation, clear damaged mitochondria, improve mitochondrial function, and ultimately reduce ROS generation;[28] and activating the Nuclear factor erythroid 2–related factor 2 (NRF2)/Heme oxygenase-1 (HO-1) signaling pathway to block intracellular ROS production and protect β-cells.[71] Second, interrupting ROS-mediated β-cell damage pathways. MSCs can block ROS signaling by inhibiting p38 MAPK signaling.[24] Third, maintaining β-cell function under stress conditions. Combined treatment with MSCs and exenatide-4 (Ex4) increases PDX-1, MafA, and forkhead box protein O1 (FoxO1) expression in β-cells.[29] FoxO1 maintains insulin secretion during metabolic stress by activating NeuroD and MafA expression.[72,73] Given the aforementioned susceptibility of β-cells to metabolic stress leading to oxidative stress, this MSC function may be crucial for sustaining β cell function under oxidative stress conditions.

In summary, the antioxidant stress-protective function of MSCs is achieved by blocking ROS production and damage pathways, as well as by maintaining β-cell function under stress conditions.

Maintaining β-Cell Homeostasis

Enhancement of Autophagy

Impaired autophagy is a significant factor contributing to β-cell dysfunction and structural damage, representing a key aspect in the pathogenesis of T2D.[74,75] MSCs primarily enhance autophagy levels by promoting autophagosome formation.

MSC-EVs overexpressing hypoxia-inducible factor 1-alpha (HIF-1α) can activate the N6-methyladenosine (m6A) reader protein YTHDF1. This activation upregulates autophagy-related proteins—including autophagy related 5(ATG5), autophagy related 2A(ATG2A), and autophagy related 14(ATG14)[76]—thereby enhancing autophagosome formation[77–79] and mediating protective autophagy to promote β-cell survival. Additionally, MSCs can upregulate expression of LAMP2 to enhance autophagosome and lysosome formation, which also represents a crucial pathway through which MSCs improve mitochondrial function and counteract oxidative stress.[28]

MSCs enhance autophagy levels through YTHDF1 and LAMP2, which is one of the key mechanisms for protecting β-cells. This not only directly mediates protective autophagy, inhibiting cell apoptosis and senescence, but also serves as an intermediate pathway for MSCs to improve mitochondrial function and counteract oxidative stress, playing a crucial role in maintaining cellular homeostasis.

Alleviation of Endoplasmic Reticulum Stress

Proinsulin possesses a complex tertiary structure with three disulfide bonds whose formation depends on the redox state within the endoplasmic reticulum (ER), making it prone to misfolding. The accumulation of misfolded proinsulin in β-cells leads to ER stress, rendering these cells particularly susceptible to ER stress-induced dysfunction.[9]

Severe ER stress is a significant trigger of apoptosis, with the protein kinase R-like endoplasmic reticulum kinase (PERK)/p38 MAPK pathway serving as a major signaling cascade in this process.[80] Studies have found that miRNA-21 enriched in MSC-Exos can inhibit p38 MAPK signaling, thereby protecting β-cells from apoptosis and concurrently alleviating ER stress.[24] This is because p38 MAPK is not only a downstream signal of ER stress but its activation can also induce sustained ER stress.[81]

p38 MAPK is currently the primary pathway through which MSCs alleviate endoplasmic reticulum stress, while the unfolded protein response (UPR) also shows potential in this regard. The accumulation of misfolded proteins stimulates the unfolded protein response (UPR), an adaptive homeostasis signaling pathway that mitigates stress.[9] In autophagy-deficient β-cells, a marked reduction in UPR gene expression is observable.[82] Stimulating autophagy has been demonstrated to mitigate endoplasmic reticulum stress induced by misfolded proinsulin accumulation, thereby protecting β-cells.[9] Consequently, whether MSCs can reduce misfolded proinsulin accumulation by enhancing autophagy and regulating UPR levels under ER stress conditions represents a question warranting future validation.

Preservation of Mitochondrial Function

Mitochondrial dysfunction in β-cells is a primary cause of defective insulin secretion.[83] Regulating autophagy and mitochondrial translocation are the primary mechanisms by which MSCs improve mitochondrial function. MSCs can act as mitochondrial donors, directly transferring functional mitochondria to adjacent damaged cells in inflammatory or ischemic environments, thereby rescuing aerobic respiration and protecting damaged cells.[84–86] MSCs can transfer mitochondria to co-cultured β-cells via tunnel nanotubes (TNTs) or EVs, and pancreatic tissue hypoxia promotes this process.[87]

Hypoxia induces mitochondrial oxidative stress, leading to mitochondrial dysfunction,[88] dysfunctional mitochondria produce excessive ROS, which is a significant driver of cellular senescence[89] and further exacerbates oxidative stress. Therefore, the role of MSCs as mitochondrial donors to preserve mitochondrial integrity constitutes another mechanism for protecting β-cell function under oxidative stress.

The Outcome of Intervening in Cellular Fate

Promotion of β-Cell Regeneration and Inhibition of Apoptosis

MSCs can enhance β-cell survival and alleviate functional impairment by alleviating the triggers of β-cell damage. Consequently, the aforementioned trials ultimately detected restoration of β-cell numbers or function. Additionally, MSCs and their exosomes can directly influence signaling pathways or gene expression related to β-cell repair, tissue regeneration, and apoptosis, ultimately promoting β-cell regeneration and repair while exerting anti-apoptotic effects.

MSC therapy significantly increases EGF mRNA and EGF protein expression levels in the pancreas,[90] which contributes to the recovery of β-cell function,[91,92] Additionally, MSCs promote v-Akt murine thymoma viral oncogene homolog (AKT)/ forkhead box protein A2 (FoxA2)/ PDX-1 gene expression, a key signaling pathway for β-cell regeneration. Forkhead box protein 1 (FoxO1) expression is downregulated, as FoxO1 inhibits FoxA2-dependent expression of the PDX-1 promoter by competing with FoxA2.[90,93,94] However, under oxidative stress conditions, FoxO1 plays a crucial role in maintaining β-cell function. Since MSCs combined with Ex4 upregulate FoxO1, subsequent studies should determine whether this effect originates from MSCs or Ex4. If it stems from MSCs, it remains

to be seen whether different injury environments elicit distinct responses, or whether MSCs can achieve a balance between promoting proliferation and providing protective functions.

In this regard, MSC-Exo has demonstrated particularly significant efficacy. First, MSC-Exo significantly enhances the expression of genes associated with tissue regeneration pathways in pancreatic tissue, including regenerating islet-derived protein 3 (Reg3), regenerating islet-derived protein 2 (Reg2), and amylase alpha 2B (Amy2b). Notably, Reg3 has been proven to stimulate β-cell regeneration by encoding an endogenous lectin and reducing inflammation via the Jak-Stat3 signaling pathway.[23,95] miRNAs within MSC-Exos may also promote pancreatic regeneration by modulating the Extl3-Reg-cyclin D1 pathway.[23] In terms of anti-apoptosis, MSC-Exos upregulate the expression of vascular endothelial growth factor (VEGF), the pro-survival gene Phosphatidylinositol 3-kinase (PI3K), and the anti-apoptotic gene BCL-2. VEGF is recognized as a pro-survival and anti-apoptotic factor crucial for maintaining islet mass. Concurrently, the expression of pro-apoptotic genes, including BCL-2-associated agonist of cell death (BAD) and BCL-2-associated X protein (BAX), is downregulated.[96]

Inhibition of β-Cell Ferroptosis

Ferroptosis is defined as an iron-dependent form of cell death initiated by excessive lipid peroxidation, leading to membrane damage.[97] Glutathione peroxidase 4 (GPX4) is a central inhibitor of ferroptosis; its inhibition induces ferroptosis and consequently impairs islet function.[98,99] Compared to other tissues, pancreatic islets express relatively low levels of GPX4, rendering them particularly susceptible to ferroptosis and subsequent functional impairment.[100]

NRF2 is a master transcriptional regulator that protects cells against ferroptosis. It controls the expression of numerous genes integral to glutathione (GSH) synthesis and metabolism, including solute carrier family 7 member 11 (SLC7A11), and can upregulate GPX4 expression.[101–103] Knockdown of SLC7A11 induces ferroptosis.[104] The key mechanism by which MSC-exo inhibits β-cell ferroptosis lies in activating NRF2 through modulation of the AKT/Extracellular signal–regulated kinase (ERK) signaling pathway,[105] thereby influencing the levels of SLC7A11 and GPX4.

Interplay Among Mechanisms and the Holistic Regulation by MSCs

Research indicates that MSCs exert their therapeutic effects not through a single pathway, but via a multi-target intervention network. This network operates comprehensively to maintain β-cell homeostasis and function, ranging from directly mitigating causes of β-cell injury to enhancing its repair and proliferation capabilities (Figure 3).

Firstly, the inflammatory response and autoimmune mechanisms are inextricably linked, forming a vicious cycle. The immunosuppressive actions of MSCs directly result in increased levels of anti-inflammatory cytokines (IL-10, TGF-β) and decreased levels of pro-inflammatory cytokines (IFN-γ),[58] simultaneously ameliorating the inflammatory micro-environment.Furthermore, MSC-induced polarization of macrophages from the M1 to the M2 phenotype not only improves the inflammatory milieu but also enables the resulting M2 macrophages to directly promote β-cell proliferation by upregulating SMAD7,[44] demonstrating dual functionality in both mitigating injury and promoting regeneration. Therefore, MSCs act concurrently on both the inflammatory and immune systems, playing a crucial role at various stages of the "immune dysregulation → inflammation → β-cell damage" cascade.

Secondly, a significant "crosstalk" exists among oxidative stress, mitochondrial dysfunction, and ER stress. ROS plays a pivotal role in β-cell damage, and the enhancement of β-cell autophagy by MSCs is a key response to this entire damaging process. Mitochondria are the primary source of ROS. Under hyperglycemic conditions, enhanced mitochondrial oxidative phosphorylation in β-cells leads to excessive ROS generation, causing oxidative stress.[66,67] Excess ROS can attack mitochondria, creating a "ROS-mitochondrial damage-ROS" vicious cycle that exacerbates oxidative stress; mitochondrial damage itself is a major cause of β-cell dysfunction.[83] Oxidative stress can also disrupt the redox homeostasis within the ER, leading to massive misfolding of proinsulin and triggering ER stress.[106] Ultimately, oxidative stress, mitochondrial dysfunction, and ER stress can all induce β-cell apoptosis or dysfunction.[68,80,83] Autophagy can clear damaged mitochondria and aggregates of misfolded proteins,[28] reducing ROS production at its source and alleviating ER stress. However, in T2D, deficient autophagic activity in β-cells amplifies the detrimental effects at each of these stages. MSC intervention targets multiple junctures simultaneously: (1) It actively removes damaged mitochondria and misfolded proteins by enhancing autophagy, directly alleviating oxidative and ER stress;[76] (2) It

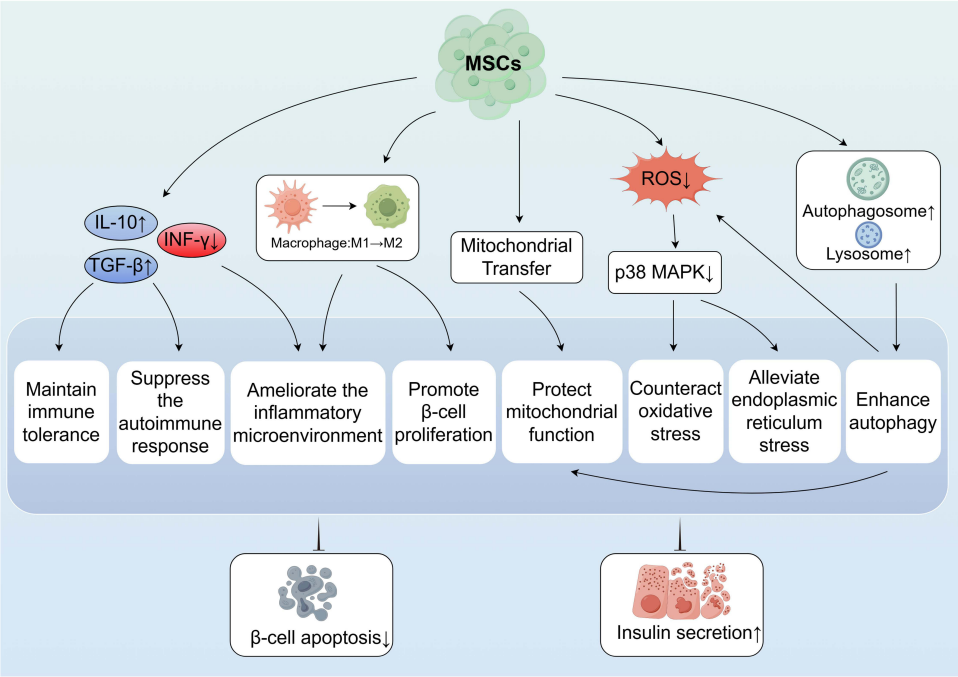

Figure 3 Interplay Among Mechanisms: MSCs improve the inflammatory microenvironment, modulate immune responses, and promote β-cell proliferation by upregulating anti-inflammatory cytokines (IL-10, TGF-β), downregulating pro-inflammatory cytokines (IFN-γ), and inducing macrophage M2 polarization. Concurrently, MSCs achieve antioxidant stress protection, mitochondrial function preservation, endoplasmic reticulum stress alleviation, and autophagy enhancement through four synergistic mechanisms: (1) enhancing autophagy to clear damaged mitochondria and misfolded proteins; (2) reducing reactive oxygen species (ROS) production; (3) transferring healthy mitochondria to β-cells; (4) inhibiting the p38 MAPK signaling pathway. Upward arrows "↑" following cytokines, signaling molecules, organelles, and physiological processes indicate promotion or increase, while downward arrows "↓" represent inhibition or decrease. Horizontal arrows "→" between M1 and M2 denote transformation. All other arrows represent progressive relationships between processes.

reduces ROS production through autophagy and other antioxidant mechanisms (activating NRF2/HO-1),[28,71] mitigating oxidative stress at its source,protecting mitochondria, and blocking downstream ROS signaling[24,96] to prevent β-cell apoptosis; (3) It directly supplements β-cells with healthy mitochondria via mitochondrial transfer,[87] reducing the occurrence of oxidative stress; (4) It employs miRNAs to inhibit p38 MAPK, a key signaling molecule in ROS damage and ER stress,[24] directly reducing the consequent β-cell apoptosis and dysfunction. Thus, MSC-mediated regulation of oxidative stress, mitochondrial dysfunction, and ER stress is a synergistic process. By enhancing protective autophagy and acting in concert with other pathways, MSCs promote the regulation of the latter three, collectively safeguarding the internal homeostasis of β-cells.

Furthermore, it is crucial to emphasize that the following signaling pathways play important roles across multiple mechanisms and are key to the holistic protection of β-cells by MSCs: (1) The NRF2 pathway is central to countering oxidative stress and inhibiting ferroptosis. As the master regulator of the cellular antioxidant response, upregulating its downstream effectors (HO-1, SLC7A11, and GPX4) can block ROS production,[71] and enhance GSH synthesis,[101] thereby combating both oxidative stress and ferroptosis.(2) The AKT pathway is critical for promoting β-cell survival. Upon activation, AKT facilitates β-cell regeneration via the AKT/FoxA2/PDX-1 axis[90] and participates in the activation of NRF2 through downstream factors like ERK, contributing to the inhibition of ferroptosis.[105] (3) The p38 MAPK/JNK pathway mediates stress and apoptosis signals. Primarily activated by ROS and ER stress,[68,80] it leads to the degradation of key β-cell transcription factors and induces apoptosis and stress.(4) The PDX-1 pathway is vital for cell regeneration and insulin expression. PDX-1 regulates both β-cell regeneration and insulin gene expression,[68,90] making it essential for normal β-cell function. However, it is susceptible to damage by oxidative stress,[68] underscoring the importance of its protection.

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Summary and Analysis of Mechanisms

The mechanisms summarized in this review vary significantly in terms of the nature of the evidence, and it is necessary to distinguish between "causality" and "correlation." Some mechanisms have established a complete causal evidence chain through approaches such as gene knockout, specific inhibitors, or gain-of-function experiments. For example, MSCs reverse β-cell dedifferentiation via IL-1Ra; blocking IL-1Ra function counteracts the effect of MSCs in increasing the expression of functional genes in β-cells within T2D islets;[26] MSC-exosomes activate NRF2 to inhibit β-cell ferroptosis by regulating the AKT/ERK signaling pathway; inhibition of AKT and ERK reversed the beneficial effects of MSC-exosomes in enhancing the expression of NRF2, GPX4, and SLC7A11.[105] The correlation is manifested by changes in certain indicators following MSC treatment occurring concurrently with improvements in β-cell function; however, there is a lack of experiments directly proving that these changes are necessary conditions. For example, while MSC treatment can effectively preserve β-cell clusters, it remains unconfirmed whether the increase in β-cell mass is due to reduced β-cell apoptosis or increased differentiation of MSCs (or the relative proportion of each).

In terms of evidence sources, definitive empirical findings specifically targeting human islet tissue or animal models of T2D include: MSCs reversing β-cell dedifferentiation via an IL-1Ra-mediated mechanism; mitochondrial transfer via TNTs or EVs; modulation of macrophage polarization and cytokine levels; reduction of ROS production; and regulation of key pathways related to cellular homeostasis or outcomes, such as LAMP2, EGF, and NRF2-key pathways related to cellular homeostasis or outcomes. Evidence that MSCs modulate the immune system and alleviate ER stress comes from T1D studies and in vitro experiments targeting β-cells, respectively. However, given that T2D patients also exhibit immune dysregulation such as Treg deficiency, and considering the central role of ER stress in β-cell damage, these mechanisms also hold significant development potential for T2D treatment.

Furthermore, during our analysis, we observed a contradiction in the role of the FoxO1 pathway: while MSC monotherapy downregulates FoxO1 to promote proliferation, the combination of MSCs and Ex4 upregulates FoxO1 to enhance stress tolerance. We tend to believe that this contradiction may stem from the bidirectional nature of the FoxO1 pathway itself: FoxO1 inhibits pancreatic duct β-cell neogenesis but maintains insulin secretion under metabolic stress.[73] The differing effects observed under MSC intervention may be due to differences in the damage environment (oxidative stress vs. normal metabolism), and we cannot rule out the influence of Ex4.

Drug-Augmenting Strategies for MSCs

Certain drugs can act on MSCs to enhance their function or protect them in adverse microenvironments, producing synergistic effects on MSCs' ability to protect β-cells. We initially focused on the potential of commonly used hypoglycemic agents in this regard, primarily because their main indication is T2D. Additionally, our emphasis on natural products stems from their low toxicity levels, factors that may facilitate clinical translation. The synergistic combination of drugs with MSCs represents a novel direction for future T2D clinical therapy, with particular emphasis on the collaborative application of hypoglycemic agents and MSCs as a key research focus.

Hypoglycemic Agents

Evidence suggests that certain hypoglycemic agents can protect or enhance MSC function through multiple mechanisms. Consequently, combination therapies utilizing both hypoglycemic agents and MSCs represent a promising new direction for the clinical treatment of T2D (Table 1).

Biguanides

Metformin (MF) can protect MSCs under hyperglycemic conditions through mechanisms such as counteracting oxidative stress and exerting anti-inflammatory effects. It activates the NRF2-glutathione peroxidase 7(GPX7) pathway, reducing ROS production and lowering oxidative stress levels in BM-MSCs cultured in high glucose.[107] Additionally, MF enhances autophagic capacity in BM-MSCs, further diminishing ROS generation.[116] Furthermore, it promotes macrophage polarization toward the anti-inflammatory M2 phenotype,[108] and reduces levels of IL-6 and TNF-α,[109] thereby protecting MSCs via its anti-inflammatory action.

Table 1 Positive Interventions of Hypoglycemic Agents on MSCs

Category	Drug	Experimental Type	Subject	Intervention and Dosage	Duration	Optimal Effective Dose	Mechanism	Outcome	Reference
Biguanides	MF	In vitro	BM-MSCs	200 μmol/L MF	NRF2, GPX7: 10 days; ROS: 24 h	N/A	NRF2↑; GPX7↑; ROS↓	Reduces oxidative stress levels in BM-MSCs under hyperglycemic conditions.	[107]
	MF	In vitro	Macrophages	0.5,2 mmol/L MF	24 h	2 mmol/L	CD206↑; Arg-1↑; IL-1β↓; TNF-α↓	Promotes macrophage polarization toward the anti-inflammatory M2 phenotype.	[108]
	MF	In vitro	AD-MSCs	5 mmol/L MF	21 days	N/A	IL-6↓; TNF-α↓	Inhibits the inflammatory response in AD-MSCs.	[109]
	MF	In vitro	PL-MSCs	0.5, 10, 40, 80, 160, 320, 640 μmol/L MF	14 days	0.5–160 μmol/L	N/A	Enhances the viability of PL-MSCs.	[110]
	MF	In vitro	BM-MSCs	10, 100 μmol/L MF	24 h	100 μmol/L	TGF-β↑; IL-10↑; Th17↓; Treg↑	Restores the immunomodulatory capacity of BM-MSCs.	[111]
Glucagon like peptide-1 receptor agonists	Liraglutide	In vitro	BM-MSCs	10 mol/L liraglutide	24h	N/A	iNOS↓; CXCL9↓; TNF-α↓; CD206↑	Suppresses M1 macrophage polarization, thereby increasing the M2/M1 ratio.	[112]
	Ex-4	In vivo	Male C57BLKS/J lar- + $Lepr^{db}$/ + $Lepr^{db}$ mice (db/db)	Ex-4 (10 μg/kg/day, s.c). and ED-71 (0.25 μg/kg, administered orally three times per week).	4 weeks	N/A	IL-1β↓; iNOS↓; CD163↑; CD206↑; TGF-β↑	Synergistically promotes M2 macrophage polarization.	[113]
		In vitro	BM-MSCs	1×10^{-8} mol/L Ex-4 and 1×10^{-9} mol/L ED-71	48h	N/A	CD163↑; CD206↑; Nos2↓; Ptgs2↓; TNF-α↓; Arg1↑; Chil3↑; Retnla↑		
	Ex-4	In vitro	AD-MSCs	20 nmol/L Ex-4	12h	N/A	PI3K/Akt-Sfrp2↑; BCL-2↑; c-IAP1/2↑; BAX↓; ROS↓; SOD↑; GSH↑	Enhances the antioxidant capacity of AD-MSCs, preserves mitochondrial function, and reduces apoptosis.	[114]
Thiazolidinediones	Pioglitazone	In vitro	AD-MSCs	5 μmol/L Pioglitazone	24h	N/A	PGC-1α↑; PrPc↑; ROS↓	Reduces ER stress and preserves mitochondrial function.	[115]

Notes: In Table 1, the upward arrow "↑" is used to represent promotion or increase, and the downward arrow "↓" represents inhibition or decrease.

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Regarding the biological activity and function of MSCs, MF enhances the viability of placenta-derived MSCs (PL-MSCs)[110] and restores the impaired immunomodulatory capacity of damaged BM-MSCs, evidenced by a decrease in Th17 cells and an increase in Tregs.[111] Pretreatment with MF also enhances the bioactivity of MSC-Exos and MSC-EVs;[117–119] however, whether this effect can be specifically targeted to β-cells requires further exploration.

By summarizing the mechanisms through which MF protects MSCs, we observe that its interventions on systems such as inflammation and immunity align with the mechanisms by which MSCs protect β-cells, including the regulation of macrophages and Treg cells. This provides evidence for their synergistic effect.

Sodium-Glucose Transporter 2 Inhibitors

In other disease contexts, pretreatment with empagliflozin has also been shown to enhance the therapeutic efficacy of MSC-Exos and MSC-EVs. However, strategies to direct these vesicles specifically to β-cells remain to be elucidated.[120,121]

Glucagon-Like Peptide-1 Receptor Agonists

In protecting MSCs, liraglutide can drive macrophage polarization from the M1 to the M2 phenotype,[112] thereby modulating the inflammatory microenvironment.Ex-4, when combined with vitamin D analog eldecalcitol (ED-71), exerts similar effects.[113] Pretreatment with Ex-4 upregulates the levels of superoxide dismutase (SOD) and GSH in AD-MSCs, protecting them under oxidative stress conditions. It also preserves mitochondrial function and reduces apoptosis.[114]

Additionally, Ex-4 can induce the expression of β-cell markers, promote the differentiation of MSCs into β-cells, and improve overall islet function.[122]

Thiazolidinediones

Pioglitazone can reduce ER stress in AD-MSCs and protect mitochondrial function.[115] It may also enhance the therapeutic efficacy of MSC-Exos through pretreatment; however, further research is required to explore the application of this effect specifically for protecting β-cells.[123]

Other Pharmacological Agents

Additionally, several other types of drugs have also demonstrated the ability to augment the therapeutic effects of MSCs (Table 2).

Trimetazidine significantly enhances the protective effect of MSCs on β-cells, improving their capacity to promote insulin secretion and inhibit β-cell apoptosis[124] Rapamycin-induced autophagy reduces ROS accumulation in MSCs, thereby safeguarding them from damage.[129] Vitamin D mitigates inflammation in AD-MSCs by lowering the levels of IL-6 and TNF-α.[109] The vitamin D analog ED-71, when combined with exenatide, promotes M2 macrophage polarization.[113] Obestatin exhibits the potential to induce the differentiation of MSCs into insulin-producing cells.[130] Dexamethasone enhances the paracrine function of MSCs.[131] Melatonin demonstrates multifaceted mechanisms in augmenting MSC function. It enhances the ability of MSC-Exos to modulate macrophage polarization,[125] upregulates the expression of superoxide dismutase 2 (SOD2) in BM-MSCs to bolster their antioxidant capacity,[126] preserves mitochondrial function in senescent MSCs,[127] and has been proven to enhance the β-cell-protective effects of MSCs in a T2D model.[128]

However, when considering the clinical application of drugs primarily targeting other systems, it is crucial to exercise caution regarding their inherent pharmacological actions and potential side effects to avoid adverse impacts on patients.

Natural Products

NPs can protect MSCs and enhance their function through multiple pathways, demonstrating significant potential in promoting MSC-mediated protection of β-cells (Table 3).

Table 2 Positive Interventions of Other Pharmacological Agents on MSCs

Drug	Experimental Type	Subject	Intervention and Dosage	Duration	Optimal Effective Dose	Mechanism	Outcome	Reference
Trimetazidine	In vitro	AD-MSCs	50 μmol/L trimetazidine	24 h/48 h	N/A	BAX↓; BCL-2↑	Enhances the protective effects of MSCs on β-cells.	[124]
Vitamin D	In vitro	AD-MSCs	10^{-6} mol/L vitamin D	21 days	N/A	IL-6↓; TNF-α↓	Suppresses the inflammatory response in AD-MSCs.	[109]
Melatonin	In vitro	BM-MSCs	1 μmol/L melatonin	48 h	N/A	PTEN/AKT↑	Augments the capacity of MSC-Exos to modulate macrophage polarization.	[125]
	In vitro	BM-MSCs	0.01, 1, 100 μmol/L melatonin	N/A	100 μmol/L	SIRT1↑; SOD2↑	Boosts the antioxidant capacity of BM-MSCs and preserves mitochondrial function.	[126]
	In vitro	AD-MSCs	1 μmol/L melatonin	24 h	N/A	HSPA1L↑; PrPc↑	Improves the autophagic clearance of damaged mitochondria in senescent MSCs.	[127]
	In vitro	UC-MSCs	10 μmol/L melatonin	7 days	N/A	PI3K/AKT ↑; KI67↑; PCNA↑; cyclin D↑; BAX↓; Capase3↓	Promotes cell proliferation and augments MSC function.	[128]

Notes: In Table 2, the upward arrow "↑" is used to represent promotion or increase, and the downward arrow "↓" represents inhibition or decrease.

Protecting MSCs from Microenvironmental Damage

The hyperglycemic environment in T2D patients can induce inflammation, oxidative stress, and other adverse conditions. Ensuring MSCs remain functional within this milieu is a prerequisite for their efficacy.

Both resveratrol and ginsenoside Rg1 exert dual anti-inflammatory and antioxidant effects. Resveratrol reduces the expression of the inflammatory cytokine IL-1β and the inflammasome NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) in MSCs by modulating the NAD-dependent deacetylase sirtuin-1 (SIRT1) and nuclear factor kappa B (NF-κB) signaling pathways, thereby mitigating inflammatory damage to MSC function.[132] Furthermore, resveratrol can improve mitochondrial function and reduce oxidative stress in BM-MSCs via the non-canonical pathway involving mitofilin.[133] An aqueous extract of traditional Chinese medicine primarily composed of ginsenoside Rg1 has been shown to decrease the expression of pro-inflammatory factors (TNF-α, IL-1β, IL-6), increase the expression of the anti-inflammatory factor IL-10, and enhance the activity of the key antioxidant component GSH,[137] indicating that ginsenoside Rg1 likely protects MSCs through both anti-inflammatory and antioxidant mechanisms.

Additionally, astragaloside IV counteracts the high glucose-induced increase in Toll-like receptor 4 (TLR4) and NF-κB p65 expression, alleviating inflammation in BM-MSCs under hyperglycemic conditions.[138] Gastrodin inhibits ROS production in BM-MSCs,[147] thereby alleviating oxidative stress.

Promoting MSC Proliferation and Differentiation

In terms of proliferation regulation, ginsenoside Rg1 (0–100 μmol/L) promotes MSC proliferation by upregulating Hypoxia-Inducible Factor 1-Alpha(HIF-1α),[137] while antler polypeptide B (molecular weight 800–1500 Da) enhances proliferation by increasing bone morphogenetic protein 7 (BMP7) expression.[139] Astragaloside IV also promotes MSC proliferation under high-glucose conditions.[138]

Regarding differentiation regulation, icariin effectively promotes BM-MSC differentiation via the mTOR/autophagy signaling pathway.[140] Quercetin has been demonstrated to promote the differentiation of BM-MSCs into β-cells and increase insulin secretion from the differentiated β-cells in vitro.[148]

Resveratrol, Asperosaponin VI, and Puerarin exert dual effects promoting both proliferation and differentiation. At low concentrations (0.1, 1, and 2.5 μmol/L), resveratrol activates SIRT1 and PCNA while inhibiting p53 and p16, thereby promoting UC-MSC proliferation. Additionally, resveratrol concentrations ranging from 0.1 to 10 μmol/L demonstrate positive effects on promoting UC-MSC differentiation.[134] Resveratrol enhances MSC differentiation capacity through pathways such as inhibiting p-NFκB p65[135] and upregulating mitofilin expression.[133] It also promotes BM-MSC proliferation and differentiation by modulating nitric oxide(NO), cyclic guanosine monophosphate(cGMP), and

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Table 3 Positive Interventions of NPs on MSCs

NPs	Origin	Experim-ental Type	Subject	Intervention and Dosage	Duration	Optimal Effective Dose	Mechanism	Outcome	Reference
Resveratrol	Reynoutria	In vitro	UC-MSCs	0, 50, 100, 200, 400 μmol/L resveratrol	1 h	200 μmol/L	SIRT1↑; NF-κb↓	Inhibits the expression of the inflammatory cytokine IL-1β and the inflammasome NLRP3 in MSCs.	[132]
		In vivo	SAMP6 mice	100 mg/kg resveratrol	2 months	N/A	Mitofilin↑	Reduces oxidative stress levels in senescent BM-MSCs, improves their mitochondrial function and transcriptional competence, and rescues their differentiation capacity.	[133]
		In vitro	UC-MSCs	0.1, 1, 2.5, 5, 10 μmol/L resveratrol	6 days	Proliferation: 2.5 μmol/L Anti-senescence: 2.5 μmol/L Differentiat-ion: 10 μmol/L	0.1, 1, 2.5 μmol/L; SIRT1↑; PCNA↑; p53↓; p16↓; 5, 10 μmol/L: SIRT1↓; PCNA↓; p53↑; p16↑	At certain concentrations, promotes cell proliferation and differentiation, while reducing cellular senescence and apoptosis.	[134]
		In vitro	Periodontal ligament MSCs (PDLSCs)	10 nmol/L resveratrol	14 days	N/A	p-NFκB p65↓; p-AMPK↑; Pgc1α↑	Promotes the formation of cell aggregates and enhances differentiation potential.	[135]
		In vitro	UC-MSCs	20 μmol/L resveratrol	12 h	N/A	PDGF-DD↑; p-ERK↑; d-caspase3↓; BAX↓; c-IAP1↑; Bcl-xl↑	Enhances the clonogenic formation capacity of UC-MSCs, drives cell proliferation, and regulates apoptosis.	[136]
Ginsenoside Rg1	Panax	In vitro	UC-MSCs	1, 5, 10, 80, 100, 150 μmol/L ginsenoside Rg1	Proliferat-ion: 24 h Differenti-ation: 21 days	Proliferation: 100μmol/L	HIF-1α↑	Promotes the proliferation and differentiation of MSCs.	[137]
Astragaloside IV	Astragalus propinquus	In vitro	BM-MSCs	10, 20, 50, 100,200 μmol/L astragaloside IV	N/A	50 μmol/L	TLR4↓; NF-kB p65 ↓	Promotes proliferation and alleviates inflammation in BM-MSCs under hyperglycemic conditions.	[138]
Antler polypeptide B	Colla cornus cervi	In vitro	BM-MSCs	1.009, 1.261, 1.578, 1.971, 2.523, 3.153, 3.942, 5.045, 6.306, 7.883×10^{-2} g/mL antler polypeptide B	72 h	1.578×10^{-2} g/mL	BMP7↑	Promotes the proliferation of BM-MSCs.	[139]
Icariin	Epimedium	In vivo	C57BL/6J mice	50 mg/kg icariin	12 weeks	N/A	PPAR-γ↓; p62 ↓; p-mTOR↓	Promotes the differentiation of BM-MSCs.	[140]
Asperosaponin VI	Dipsacus	In vitro	h-MSCs	0.01, 0.1, 1, 10, 100 mg/L asperosaponin VI	Proliferat-ion: 5 days Differenti-ation: 7 days	Proliferation: 1mg/L Differentiat-ion: 1mg/L	p-smad2/3↑; P-ERK1/2↑	Promotes the proliferation and differentiation of MSCs.	[141]
Puerarin	Pueraria	In vitro	BM-MSCs	2.5, 5, 10, 25, 50, 100 μmol/L puerarin	Proliferat-ion: 48 h Differenti-ation: 8 days	Proliferation: 10 μmol/L Differentiat-ion: 10 μmol/L	NO/cGMP/PKGII↑	Promotes the proliferation and differentiation of BM-MSCs.	[142]
Syringin	Eleutherococcus	In vitro	BM-MSCs	10, 100 μmol/L syringin	14 days	100 μmol/L	JAK2/STAT3↓; ROS/p53/p21↓	Reverses the senescent phenotype of MSCs induced by high glucose and preserves the proliferative potential of BM-MSCs.	[32]
Baicalin	Scutellaria	In vitro	BM-MSCs	5.0, 10.0, 50.0 μmol/L baicalin	N/A	50.0 μmol/L	HH↑; SHH↑; GLI-1↑; SUFU↓	Reduces apoptosis.	[143]

Lycium barbarum polysaccharide	Lycium	In vitro	BM-MSCs	0.8 mg / mL lycium barbarum polysacchari-de	24 h	N/A	LC3-II↑	Increases the number of autophagosom-es and lysosomes, restoring autophagic function.	[144]
Curcumin	Curcumin	In vivo	BALB/c mice	0.5μmol/L curcumin-treated BM-MSCs	28 days	N/A	TGFβ↑; IL1RN↑	Suppresses immune responses and induces M2 macrophage polarization.	[33]
Quercetin	Widely distributed in various plants	In vitro	BM-MSCs	0, 1, 2, 5, 10 μmol/L quercetin	24 h	2 μmol/L	ERK↑; p38 MAPK↑; VEGF↑	Promotes β-cell survival and confers resistance to apoptosis.	[145]
Asarinin	Asarum	In vitro	UC-MSCs	0.015 μmol/L asarinin	24 h	N/A	IL-2↓; IFN-γ↓; TNF-α↓; TNF-β↓; IL-4↑; IL-5↑; IL-6↑; IL-10↑	Enhances the immunomodu-latory function of UC-MSCs.	[146]
Danshensu	Salvia miltiorrhiza	In vitro	UC-MSCs	0, 50, 100, 200, 400 μmol/L danshensu	48 h	200 μmol/L	N/A	Significantly increases MSC viability and enhances the function of MSC-Exos.	[34]

Notes: In Table 3, the upward arrow "↑" is used to represent promotion or increase, and the downward arrow "↓" represents inhibition or decrease.

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extracellular signal-regulated kinase 1/2(ERK1/2).[149,150] Asperosaponin VI upregulates p-ERK1/2 and phosphorylated mothers against decapentaplegic homolog 2/3 (p-Smad2/3) expression,[141] while puerarin modulates the NO/cGMP/protein kinase G II(PKGII) pathway,[142] both promoting MSC proliferation and differentiation.

Most of the above experiments were conducted using BM-MSCs with a focus on observing their osteogenic differentiation potential. However, the proliferative mechanisms they reveal are equally applicable to enhancing the survival capacity of MSCs in a T2D environment. More importantly, the multipotent differentiation potential of MSCs suggests that the differentiation-inducing capacity of these NPs could be strategically directed toward β-cell-specific differentiation, thereby directly protecting pancreatic islet function. This translational direction warrants further exploration in subsequent studies.

Reducing MSC Senescence and Apoptosis

Syringin reverses the senescent phenotype in BM-MSCs induced by high glucose, including G0/G1 cell cycle arrest, enhanced senescence-associated beta-galactosidase (SA-β-gal) activity, and impaired cell growth.[32] Preserving the proliferative potential of MSCs under hyperglycemic conditions. Treatment with icariin also significantly reduces the expression of the senescence-associated secretory phenotype (SASP) in BM-MSCs.[151] Low concentrations of resveratrol (0.1, 1, and 2.5 μmol/L) reduce cellular senescence by stimulating SIRT1 and PCNA.[134]

Resveratrol promotes the secretion of platelet-derived growth factor-DD (PDGF-DD) in UC-MSCs, decreases the levels of cleaved caspase-3 (d-caspase3) and BAX proteins, and increases the levels of cellular inhibitor of apoptosis 1 (c-IAP1) and Bcl-xL proteins, confirming its significant anti-apoptotic effects.[136] The Hedgehog (HH) signaling pathway is critical for MSC proliferation and apoptosis. It regulates MSC proliferation and apoptosis by influencing Musashi1 (Msi1) protein expression and modulating downstream factors including c-Myc, p21, miR-148a, and miR-148b.[152] Baicalin can reduce MSC apoptosis by activating the HH signaling pathway.[143]

Modulating MSC Autophagy

Lycium barbarum polysaccharide protects damaged BM-MSCs by enhancing their autophagic activity. It promotes the formation of autophagosomes and increases lysosomal quantity, thereby restoring autophagic function in impaired cells.[144] Icariin can activate autophagy in BM-MSCs by modulating the tumor necrosis factor-alpha (TNF-α) signaling pathway, exerting notable anti-inflammatory effects and restoring cell viability.[151]

Directly Enhancing MSC Function

MSCs have been confirmed to inhibit immune responses and promote M2 macrophage polarization. Curcumin enhances this process by promoting the secretion of transforming growth factor-beta (TGF-β) and interleukin 1 receptor antagonist (IL1RN) from MSCs.[33] Quercetin activates the ERK and p38 MAPK signaling pathways, stimulating VEGF expression in BM-MSCs, which aids in β-cell repair and regeneration. The most stable promotive effect was observed at a concentration of 2 μmol/L, while effects at other concentrations fluctuated over time and sometimes fell below normal levels.[145] Pretreatment with asarinin enhances the ability of UC-MSCs to inhibit the expression of T helper 1 (Th1) cytokines (IFN-γ, TNF-α, TNF-β) and more significantly suppresses the proliferation of CD4+ and CD8+ T cells, indicating that asarinin can augment the immunomodulatory function of UC-MSCs.[146] Additionally, danshensu enhances the in vivo therapeutic efficacy of MSC-Exos,[34] and resveratrol potentiates the paracrine mechanisms of MSCs.[153]

Variation in Drug Effects and Implications

The effects of pharmacological agents on MSCs often fluctuate with changes in concentration and exposure time, and can even exert negative impacts under certain conditions. For instance, while MF generally exerts a positive effect on the viability of PL-MSCs, the optimal concentration observed at different time points in experiments varied. Furthermore, cytotoxicity was observed when its concentration exceeded 320 μmol/L.[110] At certain concentrations, resveratrol also exhibits adverse effects on MSCs. Firstly, while resveratrol promotes MSC proliferation at low doses (0.1, 1, and 2.5 μmol/L), concentrations of 5 μmol/L and above produce the opposite effect. Notably, resveratrol at 5 and 10 μmol/L still promoted UC-MSC differentiation.[134] When functioning as an antioxidant, resveratrol can reduce ROS levels in MSCs; however, its application to proliferating cells with normal ROS levels may cause DNA damage and premature

senescence.[154] Another study demonstrated that while resveratrol enhances self-renewal and multipotent differentiation potential in early-passage BM-MSCs by modulating SIRT1, it accelerates cellular senescence in late-passage BM-MSCs.[155] Quercetin activates the p38 MAPK signaling pathway to stimulate VEGF expression in BM-MSCs. However, except at a concentration of 2 μmol/L, other concentrations showed inhibition of VEGF expression or no significant difference at different time points.[145] Furthermore, p38 MAPK activation exacerbates endoplasmic reticulum stress in β-cells and reduces insulin gene expression, thereby impairing β-cell function. Therefore, when applying drugs to MSCs, careful consideration of the therapeutic objective, drug concentration, and cell passage status is essential to avoid unintended pharmacological effects.

Key Mechanisms Influencing MSC Status

In summary, certain signaling pathways are consistently recurrent in the multifaceted regulation of MSCs by pharmacological agents, suggesting their critical importance in maintaining MSC viability and function: (1) SIRT1: A central hub regulating cell metabolism, senescence, and inflammation. Melatonin activates SIRT1 and its downstream antioxidant enzymes to enhance the antioxidant capacity of MSCs.[126] Resveratrol, by activating SIRT1 and subsequently inhibiting NF-κB and p53/p16, is a key molecule concurrently achieving anti-inflammatory, anti-senescence, and pro-proliferative effects.[132,134] (2) AKT: A crucial pathway for enhancing cellular function. Ex-4 and melatonin enhance the function of MSCs or MSC-Exos via the AKT pathway.[114,125,128] (3) PrPc: A guardian of mitochondrial function. Both pioglitazone and melatonin protect mitochondrial function in MSCs by regulating cellular prion protein (PrPc).[115,127] (4) NF-κB: A classic pro-inflammatory pathway. NPs must inhibit this pathway to mitigate damage to MSCs from the inflammatory microenvironment, representing a common mechanism for protecting MSCs from inflammatory injury.[156] (5) ERK1/2: A key pathway regulating cell proliferation and differentiation. Dipsacus saponin VI and resveratrol promote MSC proliferation and differentiation by activating ERK1/2.[141,150]

Summary and Analysis of Drug Effects

The enhancement of MSC function by various drugs summarized in this section is primarily based on in vitro experiments. To date, a definitive causal relationship between the drugs, MSCs, and β-cells has not been established; therefore, the notion that drugs enhance the β-cell protective function of MSCs to treat T2D remains an indirect hypothesis. However, a comprehensive evidence chain already exists demonstrating that drugs enhance MSC function through multiple mechanisms. Consequently, this hypothesis possesses a certain degree of rationality and holds promising development prospects. We hope that our synthesis and organization will provide insights for future research and help fill the gaps in this field.

In our analysis, we identified several inconsistencies regarding the effects of these drugs. First is concentration dependence; a typical example is resveratrol, as mentioned earlier. Currently, this issue can only be addressed by clearly distinguishing between different target outcomes (proliferation vs. differentiation) to reasonably adjust concentrations. Second, quercetin activates the p38 MAPK pathway, but this pathway exacerbates endoplasmic reticulum stress in β-cells and impairs insulin secretion. We highlight this contradiction to emphasize that when using drugs for MSC pretreatment, it is essential to ensure that the drugs do not exert adverse effects on β-cells in the final therapeutic application. Finally, given the earlier mention that Ex4 may influence FoxO1, we conducted a focused literature search on Ex4; unfortunately, we have not yet been able to determine whether Ex4 regulates FoxO1 expression in β-cells during MSC therapy.

Clinical Translation and Feasibility

Although the strategy of using drugs to enhance the ability of MSCs to protect β-cell function shows great promise in theory, translating it from laboratory research into clinical treatment remains fraught with challenges.

First, the level of evidence remains insufficient. This is a major factor hindering the advancement of subsequent clinical trials and the widespread adoption of clinical applications. Among the aforementioned mechanisms, MSCs' regulation of inflammation and mitochondrial transfer function currently possess the highest level of evidence. MSC-mediated reversal of β-cell dedifferentiation via IL-1Ra, along with mitochondrial transfer through TNT or EVs, represent the few mechanisms validated in human T2D pancreatic islet tissue.[26,87] Evidence for MSCs modulating

macrophage polarization and regulating inflammatory cytokine levels originates from T2D animal models.[17,46] Additionally, MSCs exhibit high-level evidence for antioxidant stress, enhancing β-cell autophagy, promoting β-cell regeneration, anti-apoptosis, and inhibiting ferroptosis. Key pathways for these mechanisms—such as reducing ROS production, upregulating LAMP2 and EGF expression, and activating NRF2—have been validated in T2D-related animal models[28,90,105] and supported by in vitro experiments. Currently, the mechanisms by which MSCs modulate the immune system and alleviate endoplasmic reticulum stress to protect β-cells remain inconclusive. The former is because its mechanism has only been elucidated in T1D animal models or clinical trials,[58–61,65] while the latter has primarily been demonstrated through in vitro experiments.[24] Both require higher-level evidence to support their progression toward clinical translation. Most studies on the synergistic effects of drugs on MSCs have been limited to in vitro experiments, and the majority of these studies lack clear relevance to T2D. Only MF, trimetazidine, astragaloside IV, syringin, and quercetin have been tested under hyperglycemic conditions or specifically targeting β-cells.

Second, standardization of production. Clarifying production standards for MSCs from different sources is an urgent priority prior to clinical translation. There is also a lack of a unified protocol for drug-pretreated MSCs, with significant heterogeneity in the selection of drug types, concentrations, exposure times, and cell passage numbers. Furthermore, batch-to-batch variations in natural products and quality control issues further complicate standardization efforts.

Third, dose optimization. The relationship between dose and effect is complex. The effects of drugs on MSCs exhibit significant concentration- and time-dependence. The duration of drug exposure during MSC culture, the method of administration, and the metabolism and clearance of drugs within the in vivo microenvironment will all introduce new variables in clinical translation. Therefore, future studies need to further validate the relationships among these variables in T2D animal models and establish stable in vitro-in vivo pharmacokinetic-pharmacodynamic correlation models.

Fourth, delivery targeting. How to efficiently and specifically deliver MSCs or their derived extracellular vesicles (MSC-Exos/MSC-EVs) to pancreatic β-cells remains an unsolved challenge. Additionally, if the drug is intended to exert its effects in vivo without prior pretreatment, how to specifically target MSCs presents another significant challenge.

Fifth, safety. Safety concerns span multiple dimensions. First, drug residues on the surface or within the interior of MSCs may trigger off-target pharmacological effects; second, systematic studies are lacking regarding whether drug pretreatment alters the tumorigenic risk, immunogenicity, and long-term survival of MSCs. The complexity of natural products further complicates safety assessments. Existing safety data primarily stem from short-term in vitro experiments and a limited number of animal studies, with a lack of long-term safety data in humans.

Sixth, regulatory approaches. If the combination of drugs and MSCs is considered a "synergistic effect," it may require simultaneous compliance with regulations for both drugs and cell therapy products, involving joint review by multiple regulatory agencies. If drug pretreatment is regarded as part of the MSCs' in vitro culture process, it may be classified as a "post-operational cell therapy product," but proof that drug residues have been removed or rendered harmless is required, which also involves safety considerations. Exosomes or EVs derived from drug-pretreated MSCs may be developed as standalone nanomedicines, with a relatively clear regulatory pathway, though standardized production must be addressed.

Novelty and Limitations

Novelty

We have integrated eight core mechanisms into a three-tiered intervention framework: "eliminating injury triggers-maintaining cellular homeostasis-modulating cellular fate outcomes." This approach overcomes the limitations of traditional parallel listings of mechanisms, providing a clearer picture of the intervention roles of MSCs at different stages of β-cell damage and the synergistic relationships among these mechanisms. Additionally, we systematically reviewed strategies for enhancing the efficacy of MSC therapy with drugs, focusing particularly on barriers to clinical translation. Beyond summarizing the mechanisms of drug action, we critically analyzed translational challenges such as insufficient evidence levels, complex dose-response relationships, unclear regulatory pathways, and safety considerations.

Limitations

Limitations of the narrative review design: As a narrative review, although we endeavored to conduct a systematic literature search and screening process, we may not have captured all relevant studies. The absence of meta-analyses precludes quantitative integration of study effect sizes.

Heterogeneity of evidence sources: As indicated by the evidence hierarchy, there are significant differences in the quality and sources of data supporting different mechanisms. Immunomodulatory mechanisms are primarily derived from T1D models, while mechanisms for alleviating endoplasmic reticulum stress are mostly based on in vitro experiments, limiting their reliability for direct application to T2D.

Predominantly preclinical evidence: The vast majority of studies discussed in this paper, particularly those regarding drug synergism, are derived from in vitro experiments or animal models. Only a few mechanisms have been validated in human T2D islet tissues. Clinical data on MSC therapy for T2D remain scarce, and its long-term safety and efficacy in humans have yet to be established.

Insufficient exploration of MSC source heterogeneity: While we acknowledge that MSCs from different tissue sources may possess distinct functional characteristics, a systematic comparison of their mechanisms is beyond the scope of this review due to the lack of comparative studies. This represents a significant knowledge gap.

Uncertainties in clinical translation: Although drug strategies hold great promise, they face significant barriers to translation. The concentration-dependent "bidirectional effects" observed with compounds such as resveratrol and quercetin, the lack of standardized drug pretreatment protocols, and the unclear regulatory pathways for drug-pretreated MSCs all contribute to uncertainty regarding clinical feasibility. Furthermore, since most studies on natural products do not use β-cell function as an endpoint, caution is warranted when interpreting their potential for diabetes treatment.

Definitive Conclusions and Speculative Conclusions

Definitive Conclusions

MSCs can effectively modulate the inflammatory microenvironment and promote M2 macrophage polarization in T2D animal models. MSCs can improve β-cell function through mitochondrial transfer, a mechanism validated in human islet tissue. MSCs can enhance β-cell autophagy and alleviate oxidative stress, supported by ample data from animal models. Inhibiting ferroptosis via NRF2 activation is a promising new mechanism, supported by preliminary in vivo evidence.

Speculative Conclusions

The role of MSC-mediated immune regulation in T2D remains speculative, as direct evidence is currently lacking. Although the mechanism by which MSCs alleviate endoplasmic reticulum stress is theoretically sound, it lacks sufficient in vivo validation in T2D models. The protective effects of most drug-pretreated MSCs and natural product strategies on β-cells have not yet been directly validated in the context of T2D and require targeted studies.

Discussion

We have synthesized eight core mechanisms by which MSCs protect β-cell function and discussed the significant interactions among these mechanisms. Overall, the classical pathway through which MSCs regulate inflammation remains the highest-level evidence. The protection of β-cell mitochondrial function by MSCs is also highly credible due to the high level of evidence regarding mitochondrial transfer and the regulation of autophagy. Furthermore, through the discussion of mechanism interactions, we found that the regulatory effects of MSCs on macrophage phenotype and β-cell autophagy are key components of the entire protective system. The discussion in this review regarding drugs that enhance MSC function has certain limitations, as most studies are confined to in vitro experiments and have weak associations with T2D. However, we still find that metformin, due to its multifunctional effects and high level of evidence, is currently the most promising candidate drug.

The main strength of this review lies in the development of a three-tiered intervention framework, which moves beyond the traditional model of simply listing mechanisms in parallel. The limitations primarily stem from the level of evidence; specifically, the heterogeneity of evidence sources across different mechanisms affects the generalizability of

the conclusions, the scarcity of clinical data on MSC therapy for T2D means that its long-term safety and efficacy in humans remain to be established, and there is heterogeneity in the source of MSCs across different trials.

Based on the synthesis and analysis of evidence presented in this review, the clinical translation of MSC therapy for T2D will have a profound impact on future diabetes treatment paradigms. First, MSC therapy represents a shift in treatment philosophy from "glycemic control" to "restoration of β-cell function," offering the potential for fundamental protection of β-cell function. Second, MSC therapy represents an exploration of combination treatment strategies, in which existing antidiabetic drugs can serve as "potentiators" for MSC therapy, rather than merely serving as controls or alternative options.

Perspectives

Although this review preliminarily summarizes the multifaceted mechanisms by which MSCs preserve β-cell function in T2D, several important directions warrant further exploration. Firstly, whether there are differences in the mechanisms by which MSCs from different sources protect β-cell function in T2D, and whether quantifiable "preferences" exist among these mechanisms, clarifying this would help optimize MSC therapeutic strategies for different T2D subgroups. Clarifying this will help optimize MSC-based therapeutic strategies. Secondly, MSC-Exos have been proven to carry most of the therapeutic functions of MSCs. Future research should focus on identifying the specific miRNAs, proteins, or lipids within Exos that are responsible for the key effects and exploring engineered modifications of Exo cargo to develop "customized" Exo-based therapeutics with enhanced targeting and efficacy. Furthermore, close attention must be paid to pathways with "bidirectional effects," such as FoxO1. Understanding how to precisely regulate and harness the activity of such pathways in MSC therapy is a critical focus for future research.

Most current research remains confined to in vitro studies, and the mechanisms by which MSCs target T2D and β-cells warrant further investigation. The next critical step toward clinical translation is validation in T2D animal models, including establishing pharmacokinetic profiles and safety metrics. Additionally, clarifying the regulatory framework for drug-pretreated MSCs is essential for clinical translation. In summary, research on the mechanisms by which MSCs protect β-cells has progressed from "phenomenological description" to "systemic analysis." However, substantial evidence is still required to support the clinical translation of drugs that enhance this process. It is anticipated that through multidisciplinary collaboration in areas such as engineered modification and translational medicine, MSC therapies will offer safer and more effective treatment options for T2D patients.

Abbreviations

AD-MSCs, Adipose-Derived Mesenchymal Stem Cells; AD-MSC-Exos, Adipose-Derived Mesenchymal Stem Cell-Derived Exosomes; AKT, v-Akt Murine Thymoma Viral Oncogene Homolog; Amy2b, Amylase Alpha 2B; Arg-1, Arginase-1; ATG5, autophagy related 5; ATG2A, autophagy related 2A; ATG14, autophagy related 14; BAD, BCL-2-Associated Agonist of Cell Death; BAX, BCL-2-Associated X Protein; BCL-2, B-Cell Lymphoma 2; BCL-XL, B-Cell Lymphoma-Extra Large; BM-MSCs, Bone Marrow-Derived Mesenchymal Stem Cells; EGF, Epidermal Growth Factor; ER, Endoplasmic Reticulum; ERK, Extracellular Signal-Regulated Kinase; ESCs, Embryonic Stem Cells; EVs, Extracellular Vesicles; Ex-4, Exendin-4; FoxA2, Forkhead Box Protein A2; FoxO1, Forkhead Box Protein O1; Foxp3, Forkhead Box P3; GAD, Glutamic Acid Decarboxylase; GPX4, Glutathione Peroxidase 4; GPX7, Glutathione Peroxidase 7; GSH, Glutathione; HIF-1α, Hypoxia-Inducible Factor 1-Alpha; HO-1, Heme Oxygenase-1; IFN-γ, Interferon-Gamma; IL, Interleukin (e.g., IL-1β, IL-6, IL-10, IL-17); iPSCs, Induced Pluripotent Stem Cells; JNK, c-Jun N-Terminal Kinase; LAMP2, Lysosomal-Associated Membrane Protein 2; LDH, Lactate Dehydrogenase; MAFA, V-maf Musculoaponeurotic Fibrosarcoma Oncogene Homolog A; MAPK, Mitogen-Activated Protein Kinase; MCP-1, Monocyte Chemoattractant Protein-1; MCT-1, Monocarboxylate Transporter 1; MF, Metformin; MSCs, Mesenchymal Stem Cell; MSC-Exos, Mesenchymal Stem Cell-Derived Exosomes; MSC-EVs, Mesenchymal Stem Cell-Derived Extracellular Vesicles; MVs, Microvesicles; NeuroD, Neurogenic Differentiation Factor 1; NF-κB, Nuclear Factor Kappa B; NLRP3, NOD-, LRR- and Pyrin Domain-Containing Protein 3; NPs, Natural Products; NRF2, Nuclear Factor Erythroid 2–Related Factor 2; PDX-1, Pancreatic and Duodenal Homeobox 1; PGE2, Prostaglandin E2; PI3K, Phosphatidylinositol 3-Kinase; PL-MSCs, Placenta-Derived Mesenchymal Stem Cells; p38 MAPK, p38 Mitogen-

Activated Protein Kinase; Reg2, Regenerating Islet-Derived Protein 2; Reg3, Regenerating Islet-Derived Protein 3; ROS, Reactive Oxygen Species; SASP, Senescence-Associated Secretory Phenotype; SIRT1, NAD-Dependent Deacetylase Sirtuin-1; SLC7A11, Solute Carrier Family 7 Member 11; SMAD7, SMAD Family Member 7; SOD, Superoxide Dismutase; T1D, Type 1 Diabetes; T2D, Type 2 Diabetes; TGF-β, Transforming Growth Factor-Beta; Th17, T Helper 17 Cells; TNF-α, Tumor Necrosis Factor-Alpha; TNTs, Tunneling Nanotubes; Tregs, Regulatory T Cells; UC-MSCs, Umbilical Cord-Derived Mesenchymal Stem Cells; UPR, Unfolded Protein Response, VEGF, Vascular Endothelial Growth Factor.

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Author Contributions

Kunlu Wang: Writing-original draft JiuWei Li: Writing-review and editing Cong Han: Writing-review and editing, Funding acquisition Jie Li:Writing-review and editing, Funding acquisition, Supervision. 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.

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Disclosure

The authors declare that they have no competing interests in this work.

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