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Mechanisms of Ferroptosis in Pancreatic β-Cell Dysfunction in Diabetes and Exploration of Therapeutic Targets

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Abstract: Diabetes mellitus is a highly prevalent chronic metabolic disease worldwide, with progressive pancreatic β-cell dysfunction recognized as the core pathological driver of disease onset and deterioration. Accumulating evidence over the past decade has identified ferroptosis, a novel iron-dependent form of regulated cell death, as a critical mediator of pancreatic β-cell injury in both type 1 and type 2 diabetes. Ferroptosis is triggered by intracellular iron overload, excessive lipid peroxidation, and impaired antioxidant defense systems, and its dysregulation has emerged as a key research focus in the field of diabetes pathogenesis. In this review, we systematically outline the core biological characteristics and canonical regulatory networks of ferroptosis, and elaborate the pathophysiological basis of pancreatic β-cell dysfunction in diabetes. We comprehensively dissect the multifaceted mechanisms by which ferroptosis drives β-cell impairment, including iron metabolism disorder, lipid peroxidation accumulation, glutathione-GPX4 antioxidant system imbalance, and the crosstalk between ferroptosis and other cellular stress pathways. Furthermore, we integrate the latest preclinical and clinical research advances from 2025 to 2026, summarize potential therapeutic targets and intervention strategies targeting ferroptosis to preserve β-cell function, and provide a critical evaluation of the feasibility, challenges, and clinical translation potential of these strategies. Finally, we highlight the unresolved key scientific questions in current research, propose concrete and actionable future research directions, and aim to provide a theoretical framework for the development of novel diabetes treatments targeting ferroptosis-mediated β-cell injury.

Key words: Ferroptosis, diabetes mellitus, pancreatic β-cells, dysfunction, therapeutic targets.

1. Introduction

With the extension of global life expectancy and the prevalence of sedentary, high-calorie lifestyles, diabetes mellitus has become a major global public health crisis, affecting more than 500 million individuals worldwide. Notably, the prevalence of type 2 diabetes mellitus (T2DM) in young adults in China has shown a rapid upward trend in recent years, bringing severe challenges to disease prevention and management [1]. The core pathological feature of diabetes is chronic hyperglycemia, which can induce a series of serious microvascular and macrovascular complications, including cardiovascular disease, diabetic nephropathy, retinopathy, and peripheral neuropathy. These complications not only significantly reduce the quality of life of patients, but also increase the risk of all-cause mortality, and impose a heavy economic burden on global healthcare systems [2]. Existing clinical treatments for diabetes mainly focus on blood glucose regulation, which can delay disease progression to a certain extent, but fail to reverse the progressive loss of functional pancreatic β-cell mass and restore normal β-cell function in most patients. Therefore, it is urgent to explore the core molecular mechanisms of pancreatic β-cell injury, and develop disease-modifying treatments targeting the root cause of β-cell dysfunction.

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Pancreatic β-cells are the core endocrine cells in the body responsible for blood glucose homeostasis. They sense blood glucose fluctuations in real time, secrete insulin in a glucose-dependent manner, and maintain the balance of systemic glucose and lipid metabolism [3]. In the diabetic microenvironment, pancreatic β-cells are continuously attacked by multiple pathological factors, including glucolipotoxicity, chronic low-grade inflammation, and oxidative stress. Long-term exposure to these insults leads to progressive β-cell deterioration, manifested as impaired glucose-stimulated insulin secretion (GSIS), abnormal cell cycle regulation, increased cell death, and loss of mature β-cell phenotype via dedifferentiation [4]. For decades, apoptosis was considered the dominant form of β-cell death in diabetes. However, in recent years, accumulating studies have confirmed that other forms of regulated cell death, including autophagy, pyroptosis, necroptosis, and ferroptosis, also play critical non-redundant roles in the progression of β-cell failure and diabetes [5]. Among them, ferroptosis, driven by iron overload and unrestricted intracellular lipid peroxidation, has been identified as a key mediator of β-cell injury, and has become a promising research hotspot for diabetes treatment.

Ferroptosis was first named and defined as a unique form of regulated cell death by the Stockwell laboratory in 2012, which is morphologically, biochemically, and genetically distinct from apoptosis, necrosis, and other cell death modes. Ferroptosis is strictly iron-dependent, with core characteristics including excessive accumulation of lipid peroxides, depletion of intracellular glutathione (GSH), and functional inactivation of glutathione peroxidase 4 (GPX4), the core antioxidant enzyme against lipid peroxidation [6]. Pancreatic β-cells are inherently more susceptible to ferroptotic injury: their cell membranes are rich in polyunsaturated fatty acids (PUFAs) which are highly prone to oxidation, while their endogenous antioxidant enzyme expression is relatively low, leading to weak intrinsic antioxidant capacity [7]. In addition, the impaired iron handling mechanism of β-cells under diabetic conditions further promotes toxic free iron accumulation. This notion is supported by population-based studies: diabetic patients generally have significantly elevated serum ferritin levels, which are positively correlated with the risk of diabetes onset and progression [8]. In vitro and in vivo experiments have also confirmed that diabetic β-cells present classic ferroptosis hallmarks, including intracellular iron overload, accumulation of oxidized lipids, and decreased GPX4 activity; meanwhile, pharmacological or genetic inhibition of ferroptosis can significantly improve β-cell function and glucose homeostasis in diabetic models [9].

Despite rapid advances in this field, there are still many critical gaps to be addressed. Most existing evidence comes from in vitro cell lines and in vivo animal models, while direct and definitive evidence of ferroptosis in pancreatic β-cells from diabetic patients is still lacking. The precise molecular network linking ferroptosis and β-cell dysfunction has not been fully elucidated, and whether the regulatory mechanisms of ferroptosis differ between different diabetes subtypes (type 1 vs. type 2 diabetes) remains unclear. In addition, most existing ferroptosis inhibitors lack pancreatic β-cell specificity, with poor bioavailability and potential off-target adverse effects, which greatly limit their clinical translation.

This review focuses on the role and regulatory mechanisms of ferroptosis in pancreatic β-cell dysfunction in diabetes, excluding the involvement of ferroptosis in other diabetic complications (such as diabetic cardiomyopathy, nephropathy, and retinopathy). We systematically elaborate the core biological characteristics and regulatory pathways of ferroptosis, dissect the pathophysiological basis of β-cell dysfunction in diabetes, and comprehensively analyze the key mechanisms by which ferroptosis drives β-cell injury. We further summarize potential therapeutic targets and intervention strategies targeting

ferroptosis to preserve β-cell function, with a special focus on the latest research advances from 2025 to 2026. Finally, we critically evaluate the limitations of existing research, highlight unresolved key scientific questions, and propose actionable future research directions, aiming to provide a theoretical basis for the development of novel diabetes treatments targeting ferroptosis.

1.1 Literature Search Strategy and Selection Criteria

We conducted a systematic literature search in three mainstream academic databases: PubMed, Web of Science, and Scopus, to collect relevant studies published from January 2012 (the year ferroptosis was first defined) to March 2026. The search was performed using combinations of the following keywords: ferroptosis AND pancreatic β-cells AND diabetes; iron homeostasis AND diabetes AND β-cell dysfunction; GPX4 inhibition AND diabetic pathology AND ferroptotic cell death; lipid peroxidation AND β-cell failure AND diabetes mellitus; ferroptosis inhibitors AND diabetes treatment AND islet function.

1.1.1 Inclusion Criteria

Peer-reviewed original research articles and systematic reviews published in English;

Studies investigating the causal relationship between ferroptosis and pancreatic β-cell dysfunction in diabetes;

Studies including in vitro cell experiments (pancreatic β-cell lines or primary islet cells), in vivo animal models of diabetes, or human clinical studies/cohort studies;

Studies exploring the regulatory mechanisms of ferroptosis in β-cells or the therapeutic effects of ferroptosis-targeted interventions on β-cell function.

1.1.2 Exclusion Criteria

Non-English articles, conference abstracts without full text, letters, editorials, and expert opinions without original experimental data;

Studies only focusing on ferroptosis in diabetic complications without investigating pancreatic β-cell changes;

Studies with obvious experimental design defects, irreproducible results, or high risk of bias;

Review articles with overlapping content and no additional critical analysis.

To ensure the rigor of this review, we cross-validated key findings from clinical, animal, and cellular studies, and evaluated the impact of different experimental conditions on the consistency of results. We also critically analyzed conflicting results from different studies, and discussed the limitations of current experimental models in the relevant sections.

2. Core Biological Characteristics and Regulatory Mechanisms of Ferroptosis

2.1 Core Biological Characteristics of Ferroptosis

Ferroptosis is a non-apoptotic form of regulated cell death, identified after the characterization of apoptosis, necrosis, and pyroptosis. Distinct from other cell death modalities, ferroptosis is strictly driven by iron-dependent lipid peroxidation, and its occurrence is tightly regulated by cellular iron metabolism, lipid oxidation rate, and intracellular redox homeostasis maintenance, making it a unique cell death pattern with specific biological features [10]. The core biological characteristics of ferroptosis are summarized as follows.

First, ferroptosis has an absolute dependence on iron. Intracellular ferrous iron (Fe^{2+}) catalyzes the Fenton reaction, which generates massive hydroxyl radicals (OH) and reactive oxygen species (ROS), thereby initiating the chain reaction of lipid peroxidation [11]. The Fenton reaction follows the formula: $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + \cdot OH$. When cellular iron homeostasis is disrupted, excessive accumulation of labile free iron is the prerequisite and initiating factor of ferroptosis [12]. This has been verified in diabetic models: Li et al. (2020) found that the iron chelator deferoxamine (DFO) significantly reduced intracellular iron levels in β-cells of diabetic mice, inhibited ferroptosis, and improved glucose-stimulated insulin secretion, directly confirming that iron overload is a key trigger of β-cell

ferroptosis in diabetes [13].

Second, excessive accumulation of lipid peroxidation is the hallmark event of ferroptosis. Lipid peroxidation is mainly catalyzed by enzymes including lipoxygenase (LOX) and acyl-CoA synthetase long-chain family member 4 (ACSL4), generating toxic end products such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal (4-HNE). These reactive aldehydes continuously damage the structure and function of cell membranes, eventually leading to cell death [14]. Pancreatic β-cells are particularly vulnerable to lipid peroxidation-induced ferroptosis, due to their high content of PUFAs in the cell membrane and active lipid metabolism. In the diabetic microenvironment, elevated glucolipid metabolites further amplify lipid peroxidation, making it a core driver of β-cell ferroptosis [15].

Third, redox imbalance is the core biochemical basis of ferroptosis. The tripeptide glutathione (GSH) is the most abundant endogenous antioxidant in mammalian cells, and the core defense system against lipid peroxidation in ferroptosis, which exerts its function mainly through the selenoprotein glutathione peroxidase 4 (GPX4) [16]. The initiation of ferroptosis is usually triggered by the dysfunction of the system Xc^-, a cystine/glutamate antiporter composed of SLC7A11 (solute carrier family 7 member 11) and SLC3A2 (solute carrier family 3 member 2). Impaired system Xc^- function leads to insufficient cystine uptake, reduced GSH synthesis, and subsequent GPX4 inactivation. When GPX4 function is lost, cells cannot efficiently clear lipid peroxides, leading to uncontrolled lipid peroxidation and ferroptosis [17]. Consistently, diabetic β-cells show significant GSH depletion and GPX4 activity suppression, while activation of system Xc^- or restoration of GPX4 function can effectively inhibit β-cell ferroptosis [18].

Fourth, ferroptotic cells have unique ultrastructural characteristics under transmission electron microscopy (TEM). The most prominent changes are mitochondrial shrinkage, increased mitochondrial membrane density, reduced or disappeared mitochondrial cristae, and intact cell membrane, without the formation of apoptotic bodies. These features are clearly distinct from apoptosis (characterized by nuclear chromatin condensation, apoptotic body formation, and intact mitochondrial structure) and necrosis (characterized by cell membrane rupture and intracellular content leakage) [19]. In high glucose-treated β-cells, researchers observed typical ferroptotic mitochondrial morphological changes via TEM, which were completely reversed by ferroptosis inhibitors [20].

Currently, evidence for ferroptosis in diabetic β-cell injury comes from multi-level studies, including clinical, animal, and in vitro experiments. Clinical cohort studies have found that diabetic patients have abnormal iron metabolism markers, suggesting a close association between iron dysregulation and diabetes [21]. In animal models, including db/db mice and streptozotocin (STZ)-induced diabetic mice, pancreatic islets show significant iron overload and elevated lipid peroxidation markers [22]. In vitro experiments using pancreatic β-cell lines (INS-1, MIN6, RINm5F) and primary islet cells have confirmed that high glucose, high fat, or iron overload can induce typical ferroptotic changes in β-cells [23]. However, there are still critical limitations: in vitro cell lines cannot fully recapitulate the physiological characteristics of primary human β-cells; animal models cannot fully mimic the pathological process of human T2DM; most importantly, there is still a lack of direct ultrastructural and molecular evidence of ferroptosis in pancreatic islet tissues from diabetic patients.

2.2 Core Regulatory Pathways of Ferroptosis

Ferroptosis is precisely regulated by a complex multi-pathway network, and its core regulatory axes include iron metabolism, the GSH-GPX4 antioxidant system, lipid metabolism, and oxidative stress response. Key regulatory pathways, core molecules, and their specific roles in diabetic pancreatic β-cells are summarized in Table 1.

Table 1 Core regulatory pathways and key molecules of ferroptosis in diabetic pancreatic β-cells.

Regulatory pathway	Key molecules	Functional role in diabetic β-cells
Iron metabolism regulation	DMT1, ferritin (FTH1/FTL), ferroportin (FPN)	Divalent metal transporter 1 (DMT1) mediates iron uptake, which is upregulated under diabetic conditions, promoting β-cell iron overload; ferritin is responsible for intracellular iron storage, with reduced bioavailability in diabetes; ferroportin mediates iron efflux, whose downregulation further exacerbates free iron accumulation [24].
GSH-GPX4 antioxidant pathway	SLC7A11, SLC3A2, GPX4, OTUB1	SLC7A11/SLC3A2 form the system Xc^-, which mediates cystine uptake for GSH synthesis, and its expression is significantly reduced in diabetic β-cells; GPX4 is the core enzyme that catalyzes lipid peroxide reduction, with suppressed activity in diabetes; OTUB1 stabilizes SLC7A11 protein via deubiquitination, whose dysfunction promotes β-cell ferroptosis [18, 25].
Lipid metabolism regulation	ACSL4, LOX, GST	ACSL4 promotes the activation of PUFAs, providing substrates for lipid peroxidation, and is upregulated in diabetic islets; LOX family enzymes directly catalyze PUFA peroxidation; glutathione S-transferase (GST) inhibits lipid peroxidation, with reduced activity in the diabetic microenvironment [31, 47].
Antioxidant stress response	Nrf2, HO-1	Nuclear factor erythroid 2-related factor 2 (Nrf2) is the master transcription factor of antioxidant response, which inhibits ferroptosis by activating the transcription of downstream genes including HO-1, GPX4, and SLC7A11; Nrf2 signaling is significantly impaired in diabetic β-cells [5, 45].
Other regulatory pathways	FOXO1, USP22, NFAT5, PIM1	FOXO1 promotes ferroptosis via transcriptional suppression of GPX4; USP22 inhibits ferroptosis by stabilizing SIRT1 expression; NFAT5 exacerbates β-cell ferroptosis by suppressing PRDX2 transcription; PIM1 inhibits ferroptosis via enhancing mitophagy and inactivating JNK/p38 signaling [1-3, 26].

2.2.1 Iron Metabolism Regulatory Pathway

Iron homeostasis maintenance is the core upstream driver of ferroptosis. Most extracellular iron is taken up by cells via the DMT1 system, while ferritin is responsible for intracellular iron storage and detoxification, and ferroportin (FPN) is the only known mammalian iron efflux protein that mediates the release of intracellular iron to the extracellular space [24]. In the diabetic microenvironment, impaired insulin signalling and chronic hyperglycemia upregulate DMT1 expression in β-cells, reduce ferritin bioavailability, and downregulate FPN expression, leading to severe iron metabolism imbalance. Although β-cells require a certain amount of iron for normal physiological function, their iron handling capacity is limited, and impaired iron metabolism eventually leads to the accumulation of toxic labile iron, triggering ferroptosis [21].

2.2.2 GSH-GPX4 Antioxidant Pathway

The GSH-GPX4 axis is the core endogenous defense system against ferroptosis in pancreatic β-cells. System Xc^- is the main transporter for extracellular cystine uptake, and cystine is the rate-limiting precursor for GSH synthesis. GSH acts as an essential coenzyme for GPX4, which is the only enzyme that can reduce toxic phospholipid hydroperoxides to harmless fatty alcohols in mammalian cells, thereby terminating the lipid peroxidation chain reaction [18]. The deubiquitinating enzyme OTUB1 directly binds to SLC7A11, preventing its ubiquitination and proteasomal degradation, thus maintaining the normal function of system Xc^- and inhibiting ferroptosis [25]. Studies have confirmed that in STZ-induced diabetic rodent models, the transcriptional activity of SLC7A11 in pancreatic islets is significantly reduced, accompanied by impaired OTUB1 function, decreased intracellular cystine and GSH levels, and suppressed GPX4 activity, leading to a significant weakening of the β-cell's defense against lipid peroxidation damage [25, 26].

2.2.3 Lipid Metabolism Regulatory Pathway

Lipid metabolism reprogramming is a key determinant of ferroptosis sensitivity in β-cells. Long-chain PUFAs need to be activated by ACSL4 to form PUFA-CoA, which is then incorporated into cell membrane phospholipids, providing the necessary substrates for lipid peroxidation. LOX family enzymes further catalyze the oxidation of PUFA-containing phospholipids, leading to the continuous accumulation of lipid peroxides [13]. Recent studies have found that

saturated fatty acids and ω-6 PUFAs exacerbate oxidative damage and ferroptosis in β-cells by upregulating ACSL4 activity, while ω-3 PUFAs exert a protective effect by inhibiting lipid peroxidation [13, 19]. These findings indicate that different fatty acid species can differentially regulate ferroptosis sensitivity and β-cell survival in the diabetic microenvironment.

2.2.4 Antioxidant Stress Regulatory Pathway

The endogenous antioxidant defense system, especially the Nrf2 signalling pathway, is a key negative regulator of ferroptosis in β-cells. Nrf2 is the master transcription factor that regulates cellular antioxidant response, which binds to antioxidant response elements (AREs) in the promoter region of target genes, and activates the transcription of a series of antioxidant and ferroptosis-inhibiting genes, including HO-1, GPX4, SLC7A11, and ferritin [27]. Under diabetic conditions, Nrf2 signalling in β-cells is significantly impaired, leading to the collapse of the antioxidant defense system and increased susceptibility to ferroptosis [28]. Notably, the latest 2026 study by Prasad et al. confirmed that polydatin, a natural polyphenol, can significantly activate the Nrf2-GPX4 axis, enhance the antioxidant capacity of β-cells under high glucose conditions, and effectively inhibit ferroptosis [5], providing new evidence for the Nrf2 pathway as a key therapeutic target.

2.2.5 Other Regulatory Pathways

In addition to the canonical pathways above, recent studies have identified multiple novel regulatory molecules of β-cell ferroptosis in diabetes. For example, the 2025 study by Guan et al. found that nuclear factor of activated T cells 5 (NFAT5) is upregulated in diabetic β-cells, which translocates to the nucleus and binds to the PRDX2 promoter, inhibiting PRDX2 transcription, leading to accumulated oxidative stress and enhanced ferroptosis [29]. Fan et al. (2025) demonstrated that PIM1 kinase is downregulated in high glucose-treated β-cells, and PIM1 overexpression can inactivate the JNK/p38 signalling pathway, enhance PINK1/Parkin-mediated mitophagy, clear dysfunctional mitochondria, reduce ROS production, and thus inhibit β-cell ferroptosis [30]. These latest findings have expanded the regulatory network of ferroptosis in diabetic β-cells.

Notably, the core molecular mechanisms of ferroptosis have been consistently verified in multiple experimental models. In vitro cell experiments have confirmed that genetic or pharmacological modulation of key molecules (DMT1, SLC7A11, ACSL4, Nrf2) can significantly alter the sensitivity of β-cells to ferroptosis [24, 31]. Preclinical animal studies have shown that activation of the Nrf2 signalling pathway can activate the endogenous antioxidant response, increase functional β-cell mass, and improve glucose homeostasis in diabetic models [32, 33]. Human islet tissue analysis has also confirmed that the protein levels of SLC7A11 and GPX4 are significantly downregulated in islets from diabetic donors [25]. However, there are still many unresolved questions: existing pathway analyses are mostly based on single molecular targets, lacking a comprehensive understanding of the interaction of the entire regulatory network; clinical studies have small sample sizes, making it difficult to perform detailed grouping according to disease progression or diabetes subtypes; the physiological regulatory mechanisms of most identified ferroptosis mediators in human β-cells still need further verification.

3. Pathophysiological Basis of Pancreatic β-Cell Dysfunction in Diabetes

Pancreatic β-cell dysfunction is the core pathological driver of the onset and progression of both type 1 and type 2 diabetes. The progressive loss of functional β-cell mass and secretory function directly leads to absolute or relative insulin deficiency, and subsequent chronic hyperglycemia. In this section, we systematically elaborate the core manifestations and traditional regulatory mechanisms of β-cell dysfunction in diabetes, laying a foundation for the

subsequent analysis of the role of ferroptosis in this process.

3.1 Core Manifestations of Pancreatic β-Cell Dysfunction in Diabetes

The core pathological features of β-cell dysfunction in diabetes include three interrelated aspects: impaired insulin secretion, progressive loss of β-cell mass, and β-cell dedifferentiation and phenotypic degeneration.

3.1.1 Impaired Glucose-Stimulated Insulin Secretion

Impaired insulin secretion is the earliest functional manifestation of β-cell dysfunction in diabetes. In the early stage of T2DM, patients mainly present with impaired glucose-stimulated insulin secretion (GSIS), characterized by a delayed and blunted insulin secretory response to glucose stimulation. This leads to prolonged postprandial hyperglycemia and delayed blood glucose recovery in clinical practice [5]. As the disease progresses, the basal insulin secretion capacity of β-cells is gradually lost, which impairs the regulation of hepatic glucose production and leads to progressive fasting hyperglycemia [34]. These findings have been widely verified in experimental models: STZ-induced diabetic rodent models show severe impairment of β-cell function, with almost completely lost GSIS capacity.

3.1.2 Progressive Loss of Functional β-Cell Mass

Progressive reduction of β-cell mass is the core structural basis of irreversible β-cell dysfunction in diabetes. In the diabetic microenvironment, long-term exposure to hyperglycemia, hyperlipidemia, and chronic low-grade inflammation continuously induces β-cell death, while the regenerative capacity of adult β-cells is extremely limited, leading to a gradual decline in total β-cell mass [35]. Autopsy studies have confirmed that patients with long-standing T2DM have a 30-50% reduction in pancreatic β-cell mass compared with non-diabetic individuals, accompanied by a significantly higher rate of β-cell death [5]. For a long time, apoptosis was considered the main cause of β-cell loss, but recent studies have confirmed that non-apoptotic regulated cell death, including ferroptosis, pyroptosis, and necroptosis, also play a critical role in the progressive loss of β-cell mass in diabetes. Notably, multiple preclinical studies have shown that pharmacological inhibition of ferroptosis can significantly increase functional β-cell mass and improve glycemic control in diabetic rodent models [36, 37], indicating that ferroptosis is a non-redundant driver of β-cell loss in diabetes.

3.1.3 β-cell Dedifferentiation and Phenotypic Degeneration

In addition to cell death, β-cell dedifferentiation and phenotypic degeneration are also important mechanisms of functional β-cell mass loss in diabetes. Under the pathological conditions of diabetes, the abnormal cellular microenvironment leads to the downregulation of mature β-cell marker genes (including PDX1, MAFA, and INS), and the acquisition of progenitor cell-like, mesenchymal, or other islet cell phenotypes (such as α-cell characteristics). This dedifferentiation process leads to the loss of insulin secretion capacity, even if the cells are still alive [38]. In vitro experiments have confirmed that MIN6 β-cells exposed to high glucose and high fat show a significant downregulation of PDX1 expression and upregulation of α-SMA (a mesenchymal marker), indicating obvious cellular dedifferentiation [39]. Recent studies have also found that ferroptosis is closely associated with β-cell dedifferentiation: the accumulation of lipid peroxides can downregulate the expression of mature β-cell markers, while ferroptosis inhibitors can partially reverse β-cell dedifferentiation in diabetic models, suggesting that ferroptosis not only induces β-cell death, but also promotes phenotypic degeneration of surviving β-cells.

The above manifestations of β-cell dysfunction have been consistently verified in clinical and experimental studies. Oral glucose tolerance tests (OGTT) in T2DM patients show delayed and reduced

insulin secretion peaks, while autopsy studies confirm reduced β-cell mass and dedifferentiation changes [5]. Experimental studies using db/db mice and STZ-induced diabetic models have obtained consistent results, including impaired GSIS, reduced β-cell mass, and dedifferentiation [26]. In vitro experiments using MIN6 and INS-1 cell lines have also confirmed that high glucose and high fat exposure can induce impaired insulin synthesis and changes in dedifferentiation markers [39]. However, there are still limitations in existing research: most clinical studies are cross-sectional, lacking long-term longitudinal monitoring of the dynamic changes of β-cell function in the progression of diabetes; the β-cell injury mechanism in animal models is different from the natural pathological process of human diabetes; in vitro cell experiments often use supraphysiological concentrations of glucose and fatty acids, which may overestimate the pathological effects.

3.2 Traditional Regulatory Mechanisms of Pancreatic β-Cell Dysfunction in Diabetes

The dysfunction of β-cells in diabetes is regulated by multiple pathological factors, among which oxidative stress, endoplasmic reticulum (ER) stress, inflammatory response, and mitochondrial dysfunction are traditionally recognized as the core drivers.

3.2.1 Oxidative Stress

Chronic oxidative stress is a key upstream driver of β-cell dysfunction in diabetes. Hyperglycemia, the core feature of diabetes, can induce excessive production of ROS through multiple pathways, including the mitochondrial electron transport chain, polyol pathway, and advanced glycation end product (AGE) formation. Pancreatic β-cells have inherently weak antioxidant capacity, with low expression of endogenous antioxidant enzymes (such as superoxide dismutase, catalase, and GPX4), making them extremely susceptible to ROS-induced damage. Excessive ROS can damage intracellular biological macromolecules (nucleic acids, proteins, and membrane lipids), block the insulin biosynthesis pathway, and induce β-cell death [40]. Experimental data have confirmed that islets from diabetic animal models show significantly elevated oxidative stress markers (such as MDA), while antioxidant interventions can effectively improve β-cell function. Notably, oxidative stress is not only an upstream trigger of ferroptosis, but also a downstream consequence of ferroptosis, forming a vicious cycle that exacerbates β-cell injury.

3.2.2 Endoplasmic Reticulum Stress

The endoplasmic reticulum (ER) is the main site for insulin precursor folding and post-translational modification in β-cells. Under diabetic conditions, excessive insulin synthesis demand and oxidative stress lead to the accumulation of misfolded proteins in the ER, triggering the unfolded protein response (UPR), also known as ER stress. Persistent and unresolved ER stress activates three core signalling cascades: PERK, IRE1α, and ATF6 pathways, which upregulate the expression of pro-apoptotic genes and eventually lead to β-cell death [39]. Genetic studies have confirmed that the THADA locus is a susceptibility gene for T2DM, and its encoded protein regulates ER stress in β-cells by modulating SERCA2-mediated calcium homeostasis. Recent studies have found that THADA deficiency can reduce ER stress and inhibit β-cell ferroptosis in diabetic models [39], indicating a close crosstalk between ER stress and ferroptosis in β-cell injury.

3.2.3 Inflammatory Response

Chronic low-grade inflammation in pancreatic islets, also known as “insulitis”, is an important driver of β-cell dysfunction in diabetes. In the diabetic microenvironment, a large number of macrophages and other immune cells infiltrate the islets, secreting pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). These cytokines activate the NF-κB signaling pathway in β-cells, inhibit insulin gene transcription and

biosynthesis, and exacerbate β-cell death [34]. Recent studies have further identified multiple inflammatory signaling pathways involved in β-cell injury, including TLR4/NF-κB, JAK/STAT, and STING pathways. Notably, Chen et al. (2025) found that STING activation by cytosolic DNA can trigger β-cell senescence and ferroptosis via the IRF3/NF-κB pathway [41], revealing that inflammatory signaling is also a key regulator of ferroptosis in β-cells.

3.2.4 Mitochondrial Dysfunction

Mitochondria are the core organelles for energy metabolism and ATP production in β-cells, and normal mitochondrial function is essential for GSIS. Under diabetic conditions, elevated glucose and lipid levels lead to mitochondrial structural damage, including reduced cristae density, disordered respiratory chain, and decreased ATP synthesis, which directly impairs insulin production and secretion [30]. In addition, dysfunctional mitochondria are the main source of intracellular ROS, and impaired mitochondrial function further exacerbates oxidative stress, forming a vicious cycle of mitochondrial damage-ROS production-β-cell injury [30]. Recent studies have confirmed that mitochondria are the central hub coordinating multiple forms of regulated cell death in β-cells, including apoptosis, ferroptosis, pyroptosis, and necroptosis [42]. Specifically, PIM1 can enhance PINK1/Parkin-mediated mitophagy, clear dysfunctional mitochondria, reduce ROS production, and thus inhibit β-cell ferroptosis [30], indicating that mitochondrial quality control is a key regulatory node of ferroptosis in β-cells.

The above traditional regulatory mechanisms have been widely verified in clinical and experimental studies. Islet samples from diabetic patients show significantly elevated ROS and pro-inflammatory cytokine levels, accompanied by mitochondrial structural abnormalities and ER stress activation. Similarly, islets from diabetic mouse models show enhanced ER stress markers and reduced mitochondrial transmembrane potential [28, 43]. However, there are still obvious limitations in current research: clinical trials have not confirmed a clear causal relationship between these single factors and progressive β-cell dysfunction; animal experiments targeting a single stress pathway cannot fully replicate the synergistic effect of multiple pathological factors in vivo; the artificial stress factors used in cell experiments are quite different from the natural pathological process in human diabetes.

4. Key Mechanisms of Ferroptosis Regulating Pancreatic β-Cell Dysfunction in Diabetes Mellitus

As a novel and critical regulatory mechanism of pancreatic β-cell dysfunction in diabetes, ferroptosis mediates β-cell injury through multiple interconnected pathways, including iron overload, excessive lipid peroxidation accumulation, GSH-GPX4 pathway imbalance, and crosstalk with other cellular stress pathways, forming a complex regulatory network (Fig. 1).

4.1 Iron Overload: The Initiating Factor of β-Cell Ferroptosis in the Diabetic Microenvironment

Disordered iron metabolism is the core upstream trigger of iron overload and ferroptosis in pancreatic β-cells under diabetic conditions. Insulin resistance and chronic hyperglycemia can disrupt β-cell iron homeostasis by regulating the expression of key iron metabolism molecules [24]. Clinical cohort studies have consistently found that serum ferritin levels (a marker of systemic iron stores) in T2DM patients are significantly higher than those in healthy individuals, and serum ferritin levels are positively correlated with the risk of diabetes onset and progression [21]. Animal experiments have also confirmed that the iron content in pancreatic islets of db/db diabetic mice is significantly higher than that of normal mice, accompanied by abnormal expression of iron metabolism molecules: upregulated DMT1 (iron uptake), downregulated ferroportin (iron efflux), and dysregulated ferritin expression (iron storage) [36].

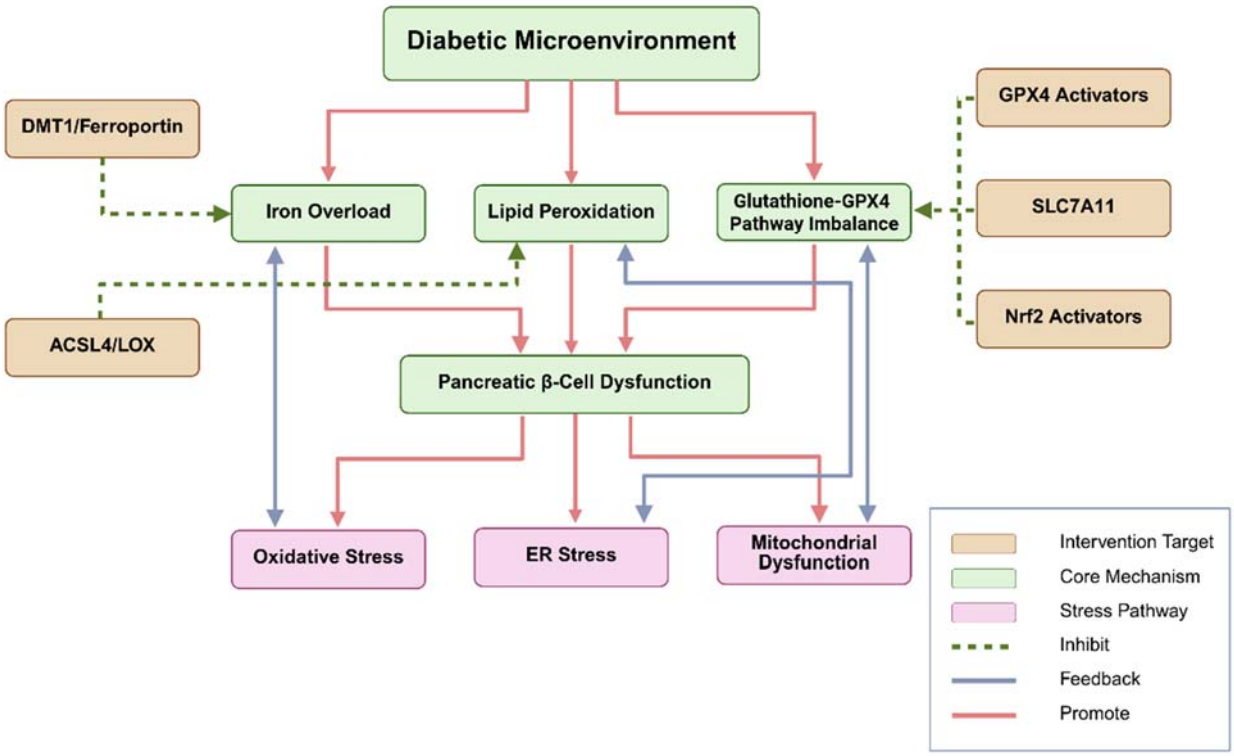

Fig. 1 Schematic diagram of ferroptosis regulating pancreatic β-cell dysfunction in diabetes.

Note: Red solid arrows indicate "promote"; green dashed arrows indicate "inhibit"; blue bidirectional arrows indicate "feedback"; targets indicate intervention targets.

Iron overload induces β-cell ferroptosis through multiple synergistic mechanisms. First, excessive free ferrous ions generate massive hydroxyl radicals via the Fenton reaction, which directly damage DNA, proteins, and membrane lipids, destroying the structural and functional integrity of β-cells [44]. Second, iron ions can directly activate the activity of lipid peroxidation-related enzymes (including LOX and ACSL4), promoting the synthesis and accumulation of lipid peroxides, the hallmark event of ferroptosis [31]. Third, iron overload can directly downregulate the expression of insulin synthesis genes (Ins1 and Ins2), impairing the secretory function of β-cells even before cell death occurs. Li et al. (2020) found that iron overload significantly downregulated Ins1/Ins2 expression in high glucose-treated INS-1 cells, which was completely reversed by the iron chelator DFO, confirming that iron overload can directly impair β-cell function independent of cell death [45].

Multi-level evidence from epidemiological, animal, and cellular studies consistently supports that iron overload is the prerequisite and initiating factor of β-cell ferroptosis in the diabetic microenvironment. However, there are still critical limitations in existing research: clinical studies lack direct pathological evidence that iron overload induces ferroptosis in human β-cells; animal experiments have not clarified the time sequence of iron metabolism disorder and β-cell dysfunction in the progression of diabetes; the iron overload induction methods used in most in vitro experiments are relatively simple, failing to replicate the physiological iron metabolism disorder in the natural progression of diabetes.

4.2 Lipid Peroxidation Accumulation: The Hallmark Event of β-Cell Ferroptosis

Pancreatic β-cells are inherently highly sensitive to lipid peroxidation-induced injury, due to their high

PUFA content in cell membranes and weak endogenous antioxidant capacity [31]. This vulnerability is further amplified in the diabetic microenvironment, where sustained glucolipotoxicity promotes continuous lipid peroxidation, forming a vicious cycle that eventually leads to the destruction of β-cell membrane integrity and functional impairment.

Different fatty acid species have differential regulatory effects on β-cell ferroptosis. Saturated fatty acids (such as palmitate) mainly promote β-cell apoptosis, while ω-6 PUFAs (such as linoleic acid, the most abundant PUFA in Western diets) are the main drivers of β-cell ferroptosis, which are activated by ACSL4 and provide abundant substrates for lipid peroxidation [31, 46]. Experimental studies have confirmed that linoleic acid treatment significantly increases lipid ROS levels and the expression of ferroptosis marker COX2 in the RINm5F β-cell line, which can be reversed by ω-3 PUFAs [31]. The end products of lipid peroxidation, including MDA and 4-HNE, induce β-cell dysfunction and death through three main pathways: (1) destabilizing the plasma membrane structure, leading to the leakage of intracellular contents; (2) modifying key proteins involved in insulin secretion, disrupting glucose sensing and insulin exocytosis; (3) triggering the ferroptotic cell death program, leading to the elimination of β-cells [34].

ACSL4 and LOX are the two core rate-limiting enzymes of lipid peroxidation in β-cell ferroptosis. ACSL4 catalyzes the esterification of long-chain PUFAs into PUFA-CoA, which is then incorporated into membrane phospholipids, generating the substrates required for lipid peroxidation. Studies have found that ACSL4 expression is significantly upregulated in pancreatic islets of diabetic mouse models, and ACSL4 inhibition can significantly reduce lipid peroxidation and ferroptosis in β-cells [26, 46]. LOX family enzymes directly catalyze the oxidation of PUFA-containing phospholipids, generating lipid hydroperoxides, which are further decomposed into toxic reactive aldehydes (MDA and 4-HNE). Pharmacological inhibition of LOX activity can effectively reduce lipid peroxidation and alleviate β-cell ferroptotic injury [47]. Notably, the latest study by Wang et al. (2025) confirmed that cynarin, a natural phenolic compound, can effectively inhibit linoleic acid-induced ferroptosis in RINm5F cells by reducing ACSL4 expression and lipid peroxidation, providing a novel natural inhibitor of β-cell ferroptosis [46].

Multi-level evidence confirms that excessive lipid peroxidation is the hallmark event and direct executioner of ferroptosis in diabetic β-cells. However, there are still limitations in current research: existing studies lack data from human islet tissues that directly link lipid peroxidation products to β-cell dysfunction in diabetic patients; most animal studies focus on the overall lipid metabolism pathway, with insufficient exploration of the specific roles of different fatty acid species; the fatty acid concentrations used in in vitro experiments are often higher than physiological levels, which may overestimate their actual biological effects in vivo.

4.3 GSH-GPX4 Pathway Imbalance: The Core Biochemical Basis of β-Cell Ferroptosis

The GSH-GPX4 axis is the core endogenous defense system against ferroptosis in pancreatic β-cells, and its dysfunction is the core biochemical basis of ferroptosis initiation in the diabetic microenvironment. The system Xc^- antiporter is responsible for the uptake of extracellular cystine, the rate-limiting precursor for GSH synthesis. Under diabetic conditions, the expression and function of system Xc^- are significantly impaired, leading to insufficient cystine uptake and reduced GSH synthesis [14]. Studies have confirmed that STZ-induced diabetic rodents show significantly reduced transcriptional activity of SLC7A11 (the functional subunit of system Xc^-) in pancreatic islets,

accompanied by a significant decrease in intracellular cystine and GSH levels [26]. In addition, excessive ROS produced under diabetic conditions accelerates GSH oxidation, further depleting intracellular GSH stores and exacerbating redox imbalance [32].

GPX4 is the only selenoprotein in mammalian cells that can reduce toxic phospholipid hydroperoxides to harmless fatty alcohols, and its function is strictly dependent on GSH as a coenzyme. Under diabetic conditions, reduced GSH levels directly lead to the inactivation of GPX4, while the transcriptional expression of GPX4 is also downregulated, resulting in the complete loss of the cell's ability to clear lipid peroxides, and the subsequent initiation of ferroptosis [18]. Studies have confirmed that GPX4 expression and activity in pancreatic islets of db/db mice are significantly lower than those of healthy mice, and genetic or pharmacological inhibition of GPX4 can directly trigger ferroptosis in β-cells, while GPX4 overexpression can significantly protect β-cells from glucose toxicity-induced injury [18]. Notably, Ding et al. (2023) found that the active form of vitamin D ($1,25\text{-}(OH)_2D_3$) can upregulate GPX4 expression via transcriptional inhibition of FOXO1, thereby inhibiting β-cell ferroptosis and improving islet function in diabetic mice [26]. The latest 2026 study by Prasad et al. further confirmed that polydatin can significantly activate the GPX4-Nrf2 axis, increase intracellular GSH levels, and effectively inhibit β-cell ferroptosis under high glucose conditions [37], providing a novel strategy to target the GSH-GPX4 pathway for β-cell protection.

In addition, the deubiquitinating enzyme OTUB1 has been identified as a novel regulator of the GSH-GPX4 pathway in β-cells. OTUB1 directly binds to SLC7A11, preventing its ubiquitination and proteasomal degradation, thus maintaining the normal function of system Xc^- and GSH synthesis. Studies have found that OTUB1 function is impaired in diabetic β-cells, leading to the downregulation of SLC7A11 and GSH depletion, which promotes ferroptosis [25].

Multi-level evidence from cellular, animal, and human tissue studies consistently supports that GSH-GPX4 pathway imbalance is the core biochemical basis of β-cell ferroptosis in diabetes. However, there are still unresolved questions: clinical studies have not fully confirmed the causal relationship between GSH-GPX4 pathway dysfunction and β-cell ferroptosis in diabetic patients; most GPX4-targeting compounds have potential non-specific interactions, and their β-cell specificity in preclinical models needs further validation; in vitro studies lack comprehensive dose-response analysis of pathway regulation, making it difficult to determine clinically applicable dose parameters.

4.4 Crosstalk Between Ferroptosis and Other Cellular Stress Pathways

Ferroptosis does not act independently in β-cell injury; instead, it extensively crosstalks with other traditional cellular stress pathways that mediate β-cell dysfunction, including oxidative stress, ER stress, mitochondrial dysfunction, and inflammatory signalling, forming an interconnected pathological network that synergistically exacerbates β-cell injury in diabetes.

4.4.1 Crosstalk Between Ferroptosis and Oxidative Stress

Oxidative stress is both an upstream trigger and a downstream consequence of ferroptosis, forming a vicious cycle in β-cells. On one hand, excessive ROS produced under diabetic conditions promotes the release of free iron from ferritin, increasing intracellular labile iron levels and activating the ferroptosis pathway. On the other hand, massive lipid peroxides produced during ferroptosis further promote ROS generation, exacerbating systemic oxidative stress in β-cells [34]. Recent studies have confirmed that ROS levels are significantly positively correlated with lipid peroxidation markers in high glucose-treated INS-1 cells; reducing ROS production can partially alleviate ferroptotic markers, while

inhibiting ferroptosis can also reduce ROS accumulation [32]. The Nrf2 pathway is the core node of this crosstalk, which simultaneously regulates cellular antioxidant response and ferroptosis, making it a key therapeutic target.

4.4.2 Crosstalk Between Ferroptosis and ER Stress

Ferroptosis and ER stress form a positive feedback loop to exacerbate β-cell injury. Persistent ER stress under diabetic conditions activates the PERK signalling pathway, which inhibits the transcription and protein expression of SLC7A11, reducing GSH synthesis and increasing β-cell susceptibility to ferroptosis [48]. Conversely, reactive lipid species produced during ferroptosis can directly damage the ER membrane structure, exacerbate the accumulation of misfolded proteins, and further amplify ER stress [34]. The T2DM susceptibility gene THADA is a key regulator of this crosstalk: THADA deficiency reduces ER stress and inhibits β-cell ferroptosis in diabetic models, while THADA overexpression exacerbates both ER stress and ferroptosis [39]. In addition, Chen et al. (2025) [49] found that STING-mediated inflammatory signalling can simultaneously activate ER stress and ferroptosis in β-cells, further expanding the crosstalk network.

4.4.3 Crosstalk Between Ferroptosis and Mitochondrial Dysfunction

Mitochondria are the central hub coordinating ferroptosis and other forms of regulated cell death in β-cells [42]. Mitochondrial dysfunction under diabetic conditions leads to excessive ROS production, which promotes iron overload and lipid peroxidation, driving ferroptosis progression. In turn, ferroptosis further destroys mitochondrial structure, reduces cristae density and mitochondrial membrane potential, impairs oxidative phosphorylation and ATP synthesis, and eventually leads to the loss of β-cell metabolic function and insulin secretion capacity [30]. Mitochondrial quality control, especially mitophagy, is a key negative regulator of this crosstalk. Fan et al. (2025) confirmed that PIM1 can inactivate the JNK/p38 signalling pathway, enhance PINK1/Parkin-mediated mitophagy, clear dysfunctional mitochondria, reduce ROS production, and thus inhibit β-cell ferroptosis [30]. This finding indicates that targeting mitochondrial quality control can simultaneously inhibit multiple cell death pathways, providing a promising strategy for β-cell protection.

4.4.3 Crosstalk Between Ferroptosis and Inflammatory Signalling

Chronic inflammatory signalling in the diabetic microenvironment can significantly promote β-cell ferroptosis, while ferroptosis can further amplify the inflammatory response, forming a vicious cycle. Pro-inflammatory cytokines (TNF-α, IL-6) secreted by infiltrating immune cells in islets can activate the NF-κB pathway in β-cells, downregulate the expression of SLC7A11 and GPX4, and increase the expression of ACSL4, thereby promoting ferroptosis [34]. Chen et al. (2025) further found that the STING-IRF3/NF-κB inflammatory pathway can directly trigger β-cell senescence and ferroptosis, revealing a novel mechanism linking inflammation and ferroptosis [49]. Conversely, the intracellular contents released by ferroptotic β-cells act as damage-associated molecular patterns (DAMPs), which can further activate immune cells and promote the secretion of pro-inflammatory cytokines, exacerbating insulitis and β-cell injury.

Existing studies have confirmed that the crosstalk between ferroptosis and other stress pathways plays a critical role in the progression of β-cell dysfunction in diabetes. However, there are still many unresolved questions: the key regulatory nodes of the crosstalk network have not been fully identified; single-target interventions show limited efficacy in animal models, as they cannot block the synergistic effect of multiple pathways; clinical studies cannot determine the temporal sequence of the activation of different pathways in the progression of human diabetes.

4.5 Key Signaling Pathways Regulating Ferroptosis in β-Cells

In addition to the canonical regulatory pathways, multiple signalling mechanisms have been identified to regulate β-cell ferroptosis by modulating the expression of ferroptosis-related molecules, among which the Nrf2, PI3K/AKT/mTOR, and non-coding RNA pathways are the most well-characterized, with promising therapeutic potential.

4.5.1 Nrf2 Signalling Pathway

The Nrf2 pathway is the master endogenous antioxidant defense system, which exerts a powerful anti-ferroptosis effect in β-cells. Nrf2 binds to AREs in the promoter region of target genes, and activates the transcription of a series of ferroptosis-inhibiting genes, including SLC7A11, GPX4, HO-1, and ferritin, thereby enhancing the antioxidant capacity of β-cells and inhibiting ferroptosis [32]. Li et al. (2024) found that grape seed proanthocyanidin extract (GCPE) can activate Nrf2 signalling, promote its nuclear translocation, upregulate the expression of GPX4 and SLC7A11, reduce intracellular iron content, and effectively inhibit ferroptosis in high glucose and high fat-treated MIN6 cells [32]. The latest 2026 study by Prasad et al. further confirmed that polydatin can significantly activate the Nrf2-GPX4 axis, enhance the antioxidant capacity of β-cells, and protect against high glucose-induced ferroptosis [28]. These findings consistently support that the Nrf2 pathway is a key therapeutic target for inhibiting β-cell ferroptosis.

4.5.2 PI3K/AKT/mTOR Signalling Pathway

The PI3K/AKT/mTOR pathway is a core regulator of cell survival, metabolism, and autophagy, which also plays an important role in regulating β-cell ferroptosis. Yang et al. (2025) [50] found that 1,8-cineole, a natural monoterpene oxide, can directly bind to the catalytic subunit of PI3K, activate the PI3K/AKT/mTOR pathway, promote autophagy to clear lipid peroxides and dysfunctional mitochondria, and thereby inhibit β-cell ferroptosis. In vivo experiments further confirmed that 1,8-cineole treatment can upregulate the phosphorylation of PI3K and AKT in pancreatic islets of HFSD/STZ-induced diabetic mice, reduce ferroptosis incidence, improve islet structure, and enhance glycemic control [50]. In addition, the PI3K/AKT/mTOR pathway can also inhibit ferroptosis by activating the Nrf2 signalling pathway, forming a synergistic antioxidant effect. These findings indicate that the PI3K/AKT/mTOR pathway is a promising target for β-cell protection via ferroptosis inhibition.

4.5.3 Non-coding RNA Regulatory Network

MicroRNAs (miRNAs) have been identified as key post-transcriptional regulators of β-cell ferroptosis, which regulate the expression of ferroptosis-related genes and affect β-cell function. Zhang et al. (2022) found that miR-144-3p is significantly upregulated in pancreatic islets of diabetic mice, which directly targets and inhibits USP22 expression, leading to reduced SIRT1 levels and subsequent β-cell ferroptosis; inhibition of miR-144-3p can restore USP22/SIRT1 signalling, inhibit ferroptosis, improve β-cell function, and enhance glycemic control in diabetic mice [51]. Wu et al. (2023) found that miR-15b-5p can inhibit GLS2 expression, reduce intracellular iron overload, and prevent β-cell ferroptosis; hispidin, a fungal metabolite, can upregulate miR-15b-5p expression and exert a protective effect against β-cell ferroptosis [52]. In addition, long non-coding RNAs and circular RNAs have also been found to regulate β-cell ferroptosis via the ceRNA mechanism, forming a complex non-coding RNA regulatory network.

4.5.4 Other Novel Signalling Pathways

Recent studies have identified multiple novel signalling pathways that regulate β-cell ferroptosis. Guan et al. (2025) found that nuclear factor of activated T cells 5 (NFAT5) is significantly upregulated in pancreatic β-cells under diabetic conditions; upon activation, NFAT5 translocates to the nucleus, directly binds to the promoter region of peroxiredoxin 2 (PRDX2), and transcriptionally

represses PRDX2 expression, thereby leading to accumulated reactive oxygen species (ROS), impaired antioxidant capacity, and enhanced ferroptosis susceptibility [29]. Conversely, β-cell-specific knockout of NFAT5 effectively upregulates PRDX2 expression, and markedly alleviates β-cell ferroptosis and functional impairment induced by high glucose and high fat stress. In addition, the c-Jun N-terminal kinase (JNK)/p38 mitogen-activated protein kinase (MAPK) pathway has been confirmed as a pro-ferroptotic cascade in β-cells, while proviral integration site for Moloney murine leukemia virus 1 (PIM1) exerts a potent anti-ferroptotic effect by inhibiting this pro-ferroptotic pathway and enhancing protective mitophagy [30]. These latest findings have greatly expanded the regulatory network of β-cell ferroptosis, shedding new light on the molecular mechanisms underlying progressive β-cell failure in both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM).

The stimulator of interferon genes (STING)-mediated innate immune signaling axis has recently emerged as a critical driver of β-cell ferroptosis in the diabetic milieu. A 2023 study by Liu et al. demonstrated that sustained hyperglycemia triggers mitochondrial DNA (mtDNA) leakage into the cytoplasm in pancreatic β-cells, which in turn activates the STING-TANK-binding kinase 1 (TBK1)-interferon regulatory factor 3 (IRF3) signalling cascade [43]. Activated IRF3 translocates to the nucleus and directly transcriptionally represses solute carrier family 7 member 11 (SLC7A11), the core functional subunit of the cystine/glutamate antiporter system Xc^-. This repression leads to impaired cystine uptake, intracellular glutathione (GSH) depletion, and subsequent inactivation of glutathione peroxidase 4 (GPX4, the central negative regulator of ferroptosis), ultimately resulting in massive lipid peroxidation and ferroptotic cell death. Consistently, β-cell-specific STING knockout in db/db mice markedly restored SLC7A11 and GPX4 expression, mitigated β-cell ferroptosis, improved glucose-stimulated insulin secretion (GSIS), and alleviated fasting hyperglycemia. Notably, this study also revealed a synergistic positive feedback loop between STING signalling and the aforementioned NFAT5 pathway: NFAT5 can directly bind to the STING promoter and enhance its transcriptional activity, further amplifying oxidative stress and ferroptotic damage in β-cells under chronic diabetic stress [43].

The AMP-activated protein kinase (AMPK) signalling axis, a master regulator of cellular energy and redox homeostasis, exhibits context-dependent dual regulatory roles in β-cell ferroptosis, as revealed by a 2024 study from Zhang et al. [53]. Transient AMPK activation in response to mild metabolic stress exerts a robust anti-ferroptotic effect in β-cells: activated AMPK directly phosphorylates Beclin 1 to promote controlled ferritinophagy (autophagic degradation of ferritin), preventing excessive labile iron pool (LIP) expansion, while simultaneously promoting nuclear translocation of nuclear factor erythroid 2-related factor 2 (Nrf2) to enhance the transcription of a panel of antioxidant and anti-ferroptotic genes, including GPX4, SLC7A11, and ferritin heavy chain 1 (FTH1). In stark contrast, chronic AMPK hyperactivation under prolonged high glucose and hyperlipidemic conditions drives unrestricted ferritinophagy, leading to massive intracellular free iron accumulation, overwhelming lipid peroxidation, and irreversible ferroptotic cell death. This dual regulatory pattern was further validated in human islets from T2DM donors, where persistent AMPK hyperphosphorylation was positively correlated with ferroptosis markers (acyl-CoA synthetase long-chain family member 4 [ACSL4] upregulation and GPX4 downregulation) and negatively correlated with β-cell insulin secretory function [53].

In addition, the hypoxia-inducible factor 1α (HIF-1α) pathway and Hippo-Yes-associated protein

(YAP) pathway have also been identified as novel regulators of β-cell ferroptosis in recent studies. Wang et al. (2025) found that HIF-1α is significantly downregulated in islets of diabetic mice, and β-cell-specific HIF-1α overexpression can directly transcriptionally activate heme oxygenase 1 (HO-1) and ferritin, reducing intracellular labile iron levels and inhibiting ferroptosis, thereby preserving β-cell mass and function in diabetic models [46]. Conversely, YAP activation has been found to promote β-cell ferroptosis via transcriptional upregulation of ACSL4 and transferrin receptor 1 (TFR1), enhancing iron uptake and lipid peroxidation; pharmacological inhibition of YAP significantly alleviated β-cell ferroptosis and improved glucose homeostasis in streptozotocin (STZ)-induced diabetic mice [18]. Collectively, these novel signalling pathways form a complex regulatory network that precisely controls β-cell ferroptosis in the diabetic microenvironment, providing a wealth of potential therapeutic targets for diabetes intervention.

5. Therapeutic Targets and Intervention Strategies Targeting β-Cell Ferroptosis in Diabetes

Given the critical role of ferroptosis in driving pancreatic β-cell dysfunction and death in diabetes, targeting ferroptosis has emerged as a promising disease-modifying strategy to preserve functional β-cell mass, delay disease progression, and even reverse early-stage diabetes. In this section, we systematically summarize the potential therapeutic targets and intervention strategies targeting β-cell ferroptosis, with a special focus on the latest preclinical research advances from 2025 to 2026, and critically evaluate their clinical translation potential.

5.1 Targeting Iron Metabolism Disorder to Alleviate β-Cell Iron Overload

As iron overload is the initiating factor of β-cell ferroptosis, regulating iron homeostasis is the most direct upstream intervention strategy to inhibit ferroptosis. The core therapeutic targets in this axis include reducing iron uptake, enhancing iron storage, and promoting iron efflux in β-cells.

Iron chelators are the most well-studied agents targeting iron overload, which can bind to free ferrous ions and reduce the intracellular labile iron pool, thereby inhibiting the Fenton reaction and subsequent lipid peroxidation. The classic iron chelator deferoxamine (DFO) has been confirmed in multiple preclinical studies to significantly reduce intracellular iron levels in β-cells, inhibit ferroptosis, improve GSIS capacity, and increase functional β-cell mass in STZ-induced and db/db diabetic mouse models [45]. However, the clinical application of DFO is limited by its poor oral bioavailability, short half-life, and potential systemic iron deficiency-related adverse effects. In recent years, novel oral iron chelators with β-cell-targeting properties have been developed: a 2025 study by Sun et al. designed a β-cell-specific iron chelator by conjugating deferasirox (an oral iron chelator) to exendin-4, a glucagon-like peptide-1 receptor (GLP-1R) agonist that is specifically internalized by β-cells via GLP-1R. This conjugate showed significantly enhanced β-cell accumulation, effectively inhibited β-cell ferroptosis, and improved glucose homeostasis in diabetic mice, with no obvious systemic iron metabolism disturbance, providing a novel strategy for targeted iron chelation therapy [36].

In addition to iron chelation, regulating the expression of key iron metabolism molecules is another promising intervention strategy. For example, downregulating the iron uptake transporter divalent metal transporter 1 (DMT1) or upregulating the iron efflux protein ferroportin (FPN) can effectively reduce intracellular iron levels in β-cells. A 2025 study by Wang et al. found that a novel small-molecule FPN agonist can significantly increase iron efflux from β-cells, reduce intracellular labile iron levels, and inhibit high glucose-induced ferroptosis in primary human islets. In vivo experiments further confirmed

that this agonist can alleviate β-cell ferroptosis, increase functional β-cell mass, and improve glycemic control in db/db mice, with no significant adverse effects on systemic iron homeostasis [46]. In addition, enhancing ferritin expression via Nrf2 activation can also increase intracellular iron storage capacity, reduce free iron levels, and exert an anti-ferroptotic effect, which has been verified in multiple preclinical studies [32, 37].

5.2 Targeting Lipid Peroxidation to Block the Execution of β-Cell Ferroptosis

Excessive lipid peroxidation is the hallmark event and direct executioner of β-cell ferroptosis, making it a key therapeutic target for intervention. The core strategies in this axis include inhibiting the expression/activity of lipid peroxidation rate-limiting enzymes, reducing the pool of peroxidizable polyunsaturated fatty acid (PUFA) substrates, and scavenging toxic lipid peroxides.

ACSL4 and lipoxygenase (LOX) are the two core rate-limiting enzymes of lipid peroxidation in β-cell ferroptosis, and their inhibition has shown robust anti-ferroptotic effects in preclinical models. ACSL4 inhibitors, such as rosiglitazone, have been confirmed to significantly reduce lipid peroxidation and inhibit β-cell ferroptosis in high glucose and high fat-treated β-cells, while also improving insulin secretion capacity [26]. A 2025 study by Wang et al. further found that cynarin, a natural phenolic compound, can directly bind to ACSL4 and inhibit its enzymatic activity, thereby reducing the synthesis of peroxidizable PUFA-CoA, inhibiting lipid peroxidation, and protecting β-cells from ferroptotic injury. In vivo experiments confirmed that cynarin treatment can significantly improve islet function and glucose homeostasis in high-fat high-sucrose diet (HFSD)/STZ-induced diabetic mice, with good biosafety [46]. For LOX inhibition, non-specific LOX inhibitors such as baicalein have been shown to effectively reduce lipid peroxidation and alleviate β-cell ferroptosis in multiple diabetic models [47], while novel isoform-specific LOX inhibitors with higher selectivity and fewer off-target effects are currently under preclinical development.

In addition, reducing the pool of peroxidizable PUFA substrates via dietary intervention or metabolic regulation is another feasible strategy. Preclinical studies have confirmed that ω-3 PUFAs (such as eicosapentaenoic acid and docosahexaenoic acid) can replace ω-6 PUFAs in the cell membrane, reduce the content of peroxidizable substrates, and inhibit β-cell ferroptosis, while also exerting anti-inflammatory and insulin-sensitizing effects [31]. Furthermore, lipid radical-trapping antioxidants (RTAs), such as ferrostatin-1 (Fer-1) and liproxstatin-1 (Lip-1), are the most classic ferroptosis inhibitors, which can specifically scavenge lipid peroxyl radicals and terminate the lipid peroxidation chain reaction. Multiple studies have confirmed that Fer-1 and Lip-1 can effectively inhibit β-cell ferroptosis, preserve β-cell mass and function, and improve glycemic control in various diabetic animal models [25, 36]. However, the poor metabolic stability and bioavailability of these compounds limit their clinical translation, and novel RTAs with improved pharmacokinetic properties and β-cell specificity are currently being developed.

5.3 Targeting the GSH-GPX4 Antioxidant System to Restore β-Cell Anti-Ferroptotic Defense

The GSH-GPX4 axis is the core endogenous defense system against β-cell ferroptosis, and its functional restoration is a key therapeutic strategy to enhance β-cell anti-ferroptotic capacity. The core intervention targets in this axis include enhancing system Xc^- function, promoting GSH synthesis, and restoring GPX4 expression and activity.

Enhancing the expression and function of system Xc^- (the core functional subunit SLC7A11) is the most upstream strategy to restore the GSH-GPX4 axis. A 2025 study by Yoo et al. found that the

deubiquitinating enzyme OTUB1 can directly bind to SLC7A11, prevent its ubiquitination and proteasomal degradation, and maintain the normal function of system Xc^-. β-cell-specific OTUB1 overexpression significantly upregulated SLC7A11 expression, increased intracellular cystine and GSH levels, restored GPX4 activity, and inhibited β-cell ferroptosis in diabetic mice [25]. In addition, multiple small-molecule compounds and natural products have been found to upregulate SLC7A11 expression via activating the Nrf2 signalling pathway, thereby enhancing system Xc^- function and inhibiting β-cell ferroptosis, including grape seed proanthocyanidin extract, polydatin, and 1,8-cineole [32, 37, 50].

Promoting GSH synthesis and supplementing GSH precursors are another effective strategy to restore the antioxidant capacity of β-cells. N-acetylcysteine (NAC), a precursor of cysteine (the rate-limiting amino acid for GSH synthesis), has been widely used in preclinical studies to increase intracellular GSH levels, inhibit lipid peroxidation, and alleviate β-cell ferroptosis induced by high glucose and high fat [34]. However, the clinical application of NAC is limited by its poor β-cell specificity and rapid systemic metabolism. Novel cysteine prodrugs with β-cell-targeting properties are currently under development, which can specifically deliver cysteine to β-cells, enhance GSH synthesis, and exert targeted anti-ferroptotic effects.

Restoring GPX4 expression and activity is the core downstream strategy to block ferroptosis execution. GPX4 is a selenoprotein, and selenium supplementation can enhance GPX4 expression and activity in β-cells. A 2025 study by Zhao et al. found that moderate selenium supplementation can significantly upregulate GPX4 expression in pancreatic islets of diabetic mice, reduce lipid peroxidation, inhibit β-cell ferroptosis, and improve glucose homeostasis, with no obvious toxic effects [18]. In addition, multiple compounds have been found to upregulate GPX4 expression via inhibiting its transcriptional repressors: for example, $1,25\text{-}(OH)_2D_3$ can upregulate GPX4 expression via transcriptional inhibition of FOXO1, thereby inhibiting β-cell ferroptosis and improving islet function in diabetic mice [26]. Notably, the latest 2026 study by Prasad et al. confirmed that polydatin can directly bind to GPX4 and enhance its enzymatic activity, while also upregulating its expression via the Nrf2 pathway, exerting a dual protective effect against β-cell ferroptosis [37].

5.4 Targeting Key Regulatory Signaling Pathways for β-Cell Ferroptosis

Targeting the key signalling pathways that regulate β-cell ferroptosis is a promising strategy to simultaneously modulate multiple ferroptosis-related processes, exerting a comprehensive anti-ferroptotic and β-cell-protective effect. The most well-characterized pathways with clinical translation potential include the Nrf2 pathway, PI3K/AKT/mTOR pathway, STING pathway, and AMPK pathway.

The Nrf2 pathway is the master regulator of cellular antioxidant response and ferroptosis inhibition, making it the most promising therapeutic target for β-cell protection. Multiple Nrf2 activators, including synthetic compounds and natural products, have shown robust anti-ferroptotic and β-cell-protective effects in preclinical diabetic models. For example, the classic Nrf2 activator sulforaphane has been confirmed to activate Nrf2 signalling, upregulate the expression of SLC7A11, GPX4, and ferritin, inhibit β-cell ferroptosis, and improve islet function in diabetic mice [32]. The latest 2026 study by Prasad et al. further found that polydatin, a natural polyphenol, can significantly activate the Nrf2-GPX4 axis, enhance the antioxidant capacity of β-cells under high glucose conditions, and effectively inhibit ferroptosis, with good biosafety and oral bioavailability [37]. Notably, several Nrf2 activators have already been approved for clinical use in other diseases, such as

dimethyl fumarate (DMF) for multiple sclerosis, which greatly accelerates their clinical translation for diabetes treatment. Preclinical studies have confirmed that DMF can activate Nrf2 signalling in β-cells, inhibit ferroptosis, and preserve β-cell mass and function in diabetic mouse models, providing a strong basis for subsequent clinical trials.

Inhibition of the pro-ferroptotic STING signalling pathway is another promising intervention strategy. Preclinical studies have confirmed that STING knockout or pharmacological inhibition can significantly restore SLC7A11 and GPX4 expression, inhibit β-cell ferroptosis, improve GSIS capacity, and alleviate hyperglycemia in diabetic mice [43, 49]. Several STING inhibitors have already entered clinical trials for inflammatory diseases and cancer, which provides a solid foundation for their repurposing for diabetes treatment. In addition, targeting the NFAT5 pathway, the JNK/p38 MAPK pathway, and the YAP pathway has also shown significant anti-ferroptotic and β-cell-protective effects in preclinical models, providing a wealth of alternative therapeutic targets for diabetes intervention [18, 29, 30].

5.5 Repurposing of Existing Clinical Drugs for β-Cell Ferroptosis Inhibition

Drug repurposing is the fastest and most cost-effective strategy to translate ferroptosis-targeted therapy into clinical practice, as existing clinical drugs have well-characterized pharmacokinetic profiles, safety profiles, and clinical application experience. In recent years, multiple commonly used clinical drugs have been found to exert significant anti-ferroptotic and β-cell-protective effects, providing new indications for these drugs.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs), the first-line drugs for T2DM treatment, have been found to inhibit β-cell ferroptosis in addition to their well-known glucose-lowering, weight-loss, and cardiorenal protective effects. A 2025 study by Li et al. found that liraglutide, a classic GLP-1RA, can significantly activate the PI3K/AKT/Nrf2 signalling pathway in β-cells, upregulate the expression of SLC7A11 and GPX4, reduce intracellular iron overload and lipid peroxidation, and inhibit high glucose and high fat-induced β-cell ferroptosis. In vivo experiments further confirmed that liraglutide treatment can alleviate β-cell ferroptosis, increase functional β-cell mass, and improve glycemic control in db/db mice [54]. Another study found that semaglutide, a long-acting GLP-1RA, can inhibit β-cell ferroptosis via enhancing mitophagy and clearing dysfunctional mitochondria, providing a novel mechanism for its β-cell-protective effect. These findings suggest that the β-cell-protective effect of GLP-1RAs is at least partially mediated by ferroptosis inhibition, which further expands their clinical application value.

Sodium-glucose cotransporter 2 inhibitors (SGLT2is), another first-line drug class for T2DM, have also been found to exert anti-ferroptotic effects in β-cells. A 2024 study by Zhang et al. found that dapagliflozin can significantly inhibit the STING-TBK1-IRF3 signalling pathway in β-cells, restore SLC7A11 and GPX4 expression, reduce lipid peroxidation, and inhibit β-cell ferroptosis in diabetic mice [53]. In addition, empagliflozin has been found to activate the AMPK/Nrf2 signalling pathway, enhance the antioxidant capacity of β-cells, and alleviate ferroptotic injury. These findings provide novel mechanistic insights into the long-term β-cell-protective effect of SGLT2is observed in clinical trials.

In addition, thiazolidinediones (TZDs, such as rosiglitazone and pioglitazone), classic insulin sensitizers, have been found to be potent ACSL4 inhibitors, which can significantly reduce lipid peroxidation and inhibit β-cell ferroptosis [8]. Vitamin D, a commonly used nutritional supplement, has been found to upregulate GPX4 expression via inhibiting FOXO1, thereby inhibiting β-cell ferroptosis. These

existing clinical drugs and supplements have good safety profiles and clinical application experience, and can quickly enter clinical trials to verify their efficacy in inhibiting β-cell ferroptosis and preserving islet function in diabetic patients.

5.6 Natural Products with Anti-Ferroptotic and β-Cell-Protective Effects

Natural products have long been an important source of novel drug development, and multiple natural compounds have been found to exert significant anti-ferroptotic and β-cell-protective effects via multiple mechanisms, with good biosafety and oral bioavailability. These natural products provide a rich library for the development of novel ferroptosis inhibitors for diabetes treatment.

Polyphenols are the most well-studied natural products with anti-ferroptotic effects, which mainly exert their protective effects via activating the Nrf2 signaling pathway, scavenging ROS, and inhibiting lipid peroxidation. The latest 2026 study by Prasad et al. confirmed that polydatin, a natural polyphenol extracted from Polygonum cuspidatum, can significantly activate the Nrf2-GPX4 axis, enhance intracellular GSH levels, reduce iron overload and lipid peroxidation, and effectively inhibit β-cell ferroptosis under high glucose conditions [37]. Grape seed proanthocyanidin extract has been found to activate Nrf2 signalling, upregulate the expression of SLC7A11 and GPX4, and inhibit β-cell ferroptosis in diabetic models [32]. In addition, resveratrol, curcumin, and baicalein have also been confirmed to exert significant anti-ferroptotic and β-cell-protective effects in multiple preclinical studies.

In addition to polyphenols, terpenoids, flavonoids, and alkaloids have also been found to inhibit β-cell ferroptosis. For example, 1,8-cineole, a natural monoterpene oxide, can activate the PI3K/AKT/mTOR pathway, promote autophagy, and inhibit β-cell ferroptosis [50]. Cynarin, a phenolic acid compound extracted from artichoke, can directly inhibit ACSL4 activity, reduce lipid peroxidation, and protect β-cells from ferroptotic injury [46]. Hispidin, a fungal metabolite, can upregulate miR-15b-5p expression, inhibit glutaminase 2 (GLS2) expression, reduce intracellular iron overload, and prevent β-cell ferroptosis [52]. These natural products have good application prospects as adjuvant therapy for diabetes, and their active ingredients can be further optimized to develop novel ferroptosis inhibitors with higher potency and specificity.

6. Challenges and Future Research Directions

Despite the rapid advances in the field of β-cell ferroptosis and diabetes over the past decade, and the promising preclinical results of ferroptosis-targeted interventions, there are still many critical challenges and unresolved scientific questions that need to be addressed before these strategies can be translated into clinical practice. In this section, we systematically summarize the core limitations of current research, highlight the key unresolved scientific questions, and propose concrete and actionable future research directions.

6.1 Core Limitations of Current Research

First, the majority of existing evidence comes from in vitro cell line experiments and in vivo animal models, while direct and definitive evidence of ferroptosis in pancreatic β-cells from diabetic patients is still extremely scarce. Most in vitro studies use immortalized β-cell lines (such as MIN6, INS-1, and RINm5F), which cannot fully recapitulate the physiological characteristics, heterogeneity, and functional complexity of primary human β-cells. Animal models, including STZ-induced diabetic mice and db/db mice, cannot fully mimic the long-term natural pathological process of human T2DM, which is characterized by the synergistic effect of multiple genetic and environmental risk factors. Most importantly, there is still a lack of direct ultrastructural

evidence (via transmission electron microscopy, TEM) and molecular pathological evidence of ferroptosis in pancreatic islet tissues from diabetic patients, which is the most critical basis for confirming the clinical relevance of β-cell ferroptosis in human diabetes.

Second, most existing studies focus on single molecular targets or pathways, lacking a comprehensive understanding of the complex regulatory network of β-cell ferroptosis and the crosstalk between ferroptosis and other forms of regulated cell death. Ferroptosis does not act independently in β-cell injury; it extensively crosstalks with apoptosis, pyroptosis, necroptosis, and other cell death modalities, forming an interconnected cell death network in the diabetic microenvironment. Single-target interventions often show limited efficacy in preclinical models, as they cannot block the synergistic effect of multiple cell death pathways. In addition, the regulatory mechanisms of ferroptosis may differ between different diabetes subtypes (T1DM vs. T2DM), different disease stages, and different patient populations, which have not been fully elucidated in current research.

Third, most existing ferroptosis inhibitors lack pancreatic β-cell specificity, with poor pharmacokinetic properties and potential off-target adverse effects, which greatly limit their clinical translation. The classic ferroptosis inhibitors, such as Fer-1 and Lip-1, have poor metabolic stability and oral bioavailability, making them unsuitable for long-term clinical application. Systemic administration of iron chelators may cause systemic iron deficiency, leading to anemia, immune dysfunction, and other adverse effects. Most ferroptosis-targeted compounds act on targets that are widely expressed in multiple tissues and organs, which may cause unexpected off-target effects. For example, systemic Nrf2 activation may promote the progression of some cancers, as Nrf2 is often overactivated in tumor cells to enhance their antioxidant capacity and survival. Therefore, the development of β-cell-specific ferroptosis inhibitors with good pharmacokinetic properties and high biosafety is the core challenge for clinical translation.

Fourth, there is still a lack of standardized biomarkers for ferroptosis in β-cells, which makes it difficult to accurately monitor the occurrence and progression of ferroptosis in clinical practice, and to evaluate the efficacy of ferroptosis-targeted interventions. Currently, the diagnosis of ferroptosis mainly relies on the detection of multiple indirect markers, including intracellular iron levels, lipid peroxidation products (malondialdehyde [MDA], 4-hydroxy-2-nonenal [4-HNE]), GSH levels, and the expression of ferroptosis-related genes (ACSL4, SLC7A11, GPX4). However, these markers are not specific to ferroptosis, and can also be altered in other forms of cell death and oxidative stress-related diseases. There is an urgent need to identify and validate specific, sensitive, and non-invasive biomarkers of β-cell ferroptosis, which can be used for early screening, disease monitoring, and efficacy evaluation in clinical practice.

6.2 Key Unresolved Scientific Questions

There are several key unresolved scientific questions in the field that need to be addressed in future research:

What is the exact causal relationship between β-cell ferroptosis and the onset and progression of human diabetes? Is ferroptosis the primary driver of β-cell dysfunction, or a secondary consequence of long-term glucolipotoxicity and other pathological insults? What is the temporal sequence of ferroptosis occurrence and β-cell functional impairment in the natural progression of human diabetes?

Are there significant differences in the regulatory mechanisms of β-cell ferroptosis between T1DM and T2DM? In T1DM, which is characterized by autoimmune destruction of β-cells, what is the role of ferroptosis in β-cell death, and what is the crosstalk between ferroptosis and autoimmune inflammatory

response?

What is the cell type specificity of ferroptosis regulation in pancreatic islets? Do pancreatic α-cells, δ-cells, and other endocrine cells have the same susceptibility to ferroptosis as β-cells? What is the effect of ferroptotic β-cell death on the function of other islet cells and the islet microenvironment?

What is the long-term safety of chronic ferroptosis inhibition in vivo? Does long-term inhibition of ferroptosis affect normal physiological functions of other tissues and organs, such as the anti-tumor immune surveillance, which relies on ferroptosis to eliminate tumor cells?

Can ferroptosis-targeted interventions reverse the established β-cell dysfunction and dedifferentiation in late-stage diabetes, or can they only delay disease progression in the early stage? What is the optimal time window for ferroptosis-targeted intervention in the progression of diabetes?

6.3 Future Research Directions and Priorities

Based on the above limitations and unresolved questions, we propose the following priority future research directions: First, it is urgent to obtain direct and definitive evidence of ferroptosis in pancreatic islet tissues from diabetic patients, using high-quality human islet samples from well-characterized diabetic cohorts. Future studies should use TEM to observe the typical ferroptotic ultrastructural changes in β-cells from diabetic patients, combined with single-cell RNA sequencing, spatial transcriptomics, and proteomics to analyze the molecular characteristics of ferroptosis in human β-cells. In addition, human islet organoids and stem cell-derived β-cells should be widely used in future research, which can better recapitulate the physiological characteristics of human β-cells, and bridge the gap between animal models and human clinical application.

Second, future research should focus on the comprehensive analysis of the regulatory network of β-cell ferroptosis, and the crosstalk between ferroptosis and other cell death modalities and cellular stress pathways. Multi-omics approaches, including transcriptomics, proteomics, lipidomics, and metabolomics, should be used to systematically map the molecular network of β-cell ferroptosis in the diabetic microenvironment, and identify the core regulatory nodes that simultaneously control multiple ferroptotic processes. In addition, the synergistic effect of combined targeting of ferroptosis and other cell death pathways should be explored, which may achieve better β-cell-protective effects than single-target interventions.

Third, the development of β-cell-specific ferroptosis inhibitors with good pharmacokinetic properties and high biosafety is the top priority for clinical translation. Future drug development should focus on β-cell-targeted delivery systems, such as conjugating ferroptosis inhibitors to GLP-1R agonists, which can be specifically internalized by β-cells via GLP-1R, reducing systemic exposure and off-target adverse effects. In addition, structure-based drug design should be used to develop novel, highly selective, and metabolically stable ferroptosis inhibitors, with optimized pharmacokinetic properties suitable for long-term oral administration.

Fourth, it is urgent to identify and validate specific, sensitive, and non-invasive biomarkers of β-cell ferroptosis. Future studies should use multi-omics approaches to identify circulating biomarkers (such as circulating microRNAs, exosomal proteins, or lipid peroxidation products) that can specifically reflect the ferroptotic state of β-cells in vivo. These biomarkers can be used for early screening of high-risk populations, monitoring disease progression, and evaluating the efficacy of ferroptosis-targeted interventions in clinical trials.

Fifth, well-designed, large-scale clinical trials are needed to verify the efficacy and safety of ferroptosis-targeted interventions in diabetic patients. The existing clinical drugs with confirmed anti-ferroptotic effects in preclinical studies, such as

GLP-1RAs, SGLT2is, DMF, and vitamin D, should be prioritized for clinical trials, to verify whether they can inhibit β-cell ferroptosis, preserve islet function, and delay disease progression in diabetic patients. These clinical trials should use standardized endpoints, including changes in β-cell function (measured by C-peptide secretion), glycemic control, and the incidence of diabetes-related complications, with long-term follow-up to evaluate the safety of chronic intervention.

7. Conclusion

Progressive pancreatic β-cell dysfunction and loss of functional β-cell mass are the core pathological drivers of the onset and progression of diabetes mellitus, and there is still an urgent unmet clinical need for disease-modifying treatments that can reverse or halt this process. Over the past decade, accumulating evidence has identified ferroptosis, a novel iron-dependent form of regulated cell death driven by excessive lipid peroxidation, as a critical non-redundant mediator of β-cell injury in both T1DM and T2DM. Pancreatic β-cells are inherently highly susceptible to ferroptotic injury, due to their high PUFA content in cell membranes, weak endogenous antioxidant capacity, and impaired iron handling mechanism under diabetic conditions.

In this review, we systematically outline the core biological characteristics and canonical regulatory networks of ferroptosis, elaborate the pathophysiological basis of β-cell dysfunction in diabetes, and comprehensively dissect the multifaceted mechanisms by which ferroptosis drives β-cell impairment, including iron overload, excessive lipid peroxidation accumulation, GSH-GPX4 antioxidant system imbalance, and the extensive crosstalk between ferroptosis and other cellular stress pathways. We further integrate the latest preclinical research advances from 2025 to 2026, summarize potential therapeutic targets and intervention strategies targeting β-cell ferroptosis, including targeting iron metabolism, lipid peroxidation, the GSH-GPX4 axis, and key regulatory signalling pathways, as well as the repurposing of existing clinical drugs and the application of natural products. We also critically evaluate the core limitations of current research, highlight the key unresolved scientific questions, and propose concrete and actionable future research directions, with a focus on obtaining clinical evidence from human samples, developing β-cell-specific ferroptosis inhibitors, identifying specific biomarkers, and conducting well-designed clinical trials.

In conclusion, targeting ferroptosis represents a promising and innovative strategy to preserve functional β-cell mass and delay the progression of diabetes. With the continuous elucidation of the regulatory mechanisms of β-cell ferroptosis, and the development of novel, specific, and safe ferroptosis-targeted interventions, we believe that this strategy will eventually be translated into clinical practice, bringing new hope for the treatment of diabetes mellitus.

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