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Research Advances in Cell Injury, Cell Death and Related Inflammatory Factors in the Pathogenesis of Diabetes

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Abstract. Persistent hyperglycemia attenuates insulin secretory responses and inhibits insulin-mediated glucose transport. Chronic long-term hyperglycemia causes irreversible damage and even death of pancreatic islet β-cells. With disease progression, the number, quality and function of islet β-cells progressively decline. β-cell injury is closely associated with oxidative stress, endoplasmic reticulum stress, lipotoxicity, glucolipid metabolic disorders, mitochondrial dysfunction and abnormal insulin secretion. Multiple forms of programmed cell death are involved, including autophagy, apoptosis, ferroptosis, pyroptosis and cuproptosis. Islet cell autophagy plays a protective regulatory role in the progression of diabetes. β-cell autophagy can modulate macrophage activation and suppress T cell-mediated autoimmune responses. Inflammatory factors such as IL-1β and IL-6 participate in the development and progression of diabetes by mediating inflammatory cascades and cell death.

Keywords: Diabetes, β-cell injury, cell death, related inflammatory factors

1. Introduction

Diabetes is a metabolic disease characterized by chronic hyperglycemia, with type 2 diabetes accounting for more than 90% of cases. According to the International Diabetes Federation (IDF) Diabetes Atlas 9th Edition 2025, the global prevalence of diabetes among people aged 20–79 years reached 11.1% in 2024, with approximately 589 million cases, and is projected to rise to 13.9% by 2050. China remains the country with the largest number of diabetic patients worldwide [1], with an age-standardized prevalence of 11.9% and a total of 148 million [2] patients in 2024. A national epidemiological survey in 2023 showed that the age-standardized prevalence of diabetes in China reached 13.67%, with about 233 million cases, representing a 163% increase compared with 2005 [3]. Without effective interventions, the prevalence will continue to rise, reaching 16.15% in 2030, 21.52% in 2040 and 29.10% in 2050; the prevalence in regions such as Beijing and Tianjin may exceed 40%. Effective control of the obesity epidemic could reduce the increase in prevalence by nearly 50%, bringing the figure below 15% by 2050. Diabetes severely reduces patients' quality of life and significantly increases the risk of complications including cardiovascular disease, nephropathy, retinopathy and diabetic foot, making it a major global public health problem [4]. Diabetes shows marked heterogeneity in age, gender, region and economic status. The prevalence is higher in urban than rural areas and higher in men than women; driven by obesity, high-fat diets and

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sedentary lifestyles, the prevalence among adolescents and young adults continues to rise [3]. Generally low treatment adherence among patients results in insufficient glycemic control rates [5]. China's annual direct medical expenditure on diabetes has exceeded 600 billion yuan, and the total economic burden including indirect losses exceeds 900 billion yuan [6]. Diabetic complications are the leading causes of disability and death, severely affecting multi-organ function and long-term survival outcomes [7].

2. Pathogenesis and therapeutic approaches of diabetes

2.1. Pathogenesis

The core pathogenesis of diabetes involves insulin resistance, pancreatic islet β-cell failure and progressive reduction in β-cell mass. Molecular mechanisms include oxidative stress, chronic low-grade inflammation, endoplasmic reticulum stress, mitochondrial dysfunction, abnormal insulin signaling pathways and dysregulated programmed cell death, although the precise regulatory network remains incompletely elucidated [8].

In recent years, mitophagy, pyroptosis, ferroptosis and cuproptosis have become research hotspots. Mitophagy maintains mitochondrial homeostasis by selectively removing damaged mitochondria; its dysfunction leads to reactive oxygen species (ROS) accumulation, further inducing pyroptosis, ferroptosis and cuproptosis [9]. Pyroptosis is an inflammatory programmed death mediated by the NLRP3 inflammasome, promoting the maturation and release of IL-1β and IL-18. Ferroptosis is an iron-dependent programmed death characterized by lipid peroxidation and redox imbalance. Cuproptosis is a novel copper-dependent non-apoptotic death linked to tricarboxylic acid cycle disturbances, lipoylated protein aggregation and iron-sulfur cluster protein loss. Clinical studies confirm significantly elevated plasma and urine copper levels in diabetic patients, indicating systemic copper metabolic abnormalities. Multiple cell death pathways cross-talk and collectively drive β-cell injury and diabetes progression [10].

2.2. Therapeutic approaches

2.2.1. Chemical drugs

Biguanides: Metformin [11] (first-line agent; improves insulin sensitivity, inhibits hepatic gluconeogenesis, regulates AMPK/mTOR/autophagy). Sulfonylureas: Glibenclamide, gliclazide, glimepiride, etc. (promote insulin secretion). α-Glucosidase inhibitors: Acarbose, voglibose, miglitol (delay carbohydrate absorption; clinical utilization rate 24.4%) [12]. DPP-4 inhibitors: Sitagliptin, saxagliptin, linagliptin, alogliptin, vildagliptin, trelagliptin, etc. [12]. SGLT2 inhibitors: Empagliflozin, dapagliflozin, canagliflozin, etc. (promote urinary glucose excretion with cardio-renal protection) [13]. In the clinical drug-use structure, insulin accounts for 36.3%, α-glucosidase inhibitors 24.4%, sulfonylureas 14%, biguanides 11%, and novel agents such as DPP-4 inhibitors, GLP-1 receptor agonists and SGLT2 inhibitors are increasing annually [12].

2.2.2. Biologicals and insulin

GLP-1 receptor agonists: Liraglutide, semaglutide, dulaglutide, exenatide, loxenatide, tirzepatide, etc [14,15]. Promote insulin secretion and suppress glucagon in a glucose-dependent manner, delay gastric emptying, reduce body weight and carry low hypoglycemia risk [16]. Insulins: Aspart, lispro (rapid-acting); glargine, detemir, degludec (long-acting/ultra-long-acting) [13]. Other biologicals:

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GLP-2 receptor agonist teduglutide; amylin analogue pramlintide; SGLT1/2 dual inhibitor sotagliflozin [13].

2.2.3. Investigational drugs

With advances in diabetes pathogenesis research and the concept of precision medicine, new drug development for diabetes focuses on four core directions: precise glycemic control, preservation of islet β-cell function, reduction of complications and improvement of treatment adherence. These directions mainly include GLP-1 receptor agonists, dual/triple-target agonists, long-acting insulin preparations and islet cell therapy. Drugs under development in each category break through the limitations of traditional treatments via unique mechanisms, offering diversified and personalized options for patients at different disease stages and driving the field toward greater efficacy, safety and convenience.

Phase I investigational drugs: Focus on safety, tolerability, pharmacokinetics and preliminary hypoglycemic activity. Representative agents include IBI3032, ASC30, GZR102, E-islet 01, etc. E-islet 01 targets islet cell therapy, repairing damaged β-cells or replacing failed ones to improve insulin secretion at the pathological root, with important clinical potential for patients with severe β-cell failure.

Phase II investigational drugs: Confirm efficacy and optimize dosage. Representative agents include GZR18, LY3305677, etc. Most are GLP-1 receptor agonists or dual-target agonists, improving glycemic control, body weight and insulin resistance.

Phase III investigational drugs: Pivotal stage for large-sample, multi-center, long-term verification of efficacy and safety. Representative agents include retatrutide, CagriSema, HS-20094, etc. Retatrutide, a novel multi-target agonist, shows robust hypoglycemia, weight loss and β-cell protective effects, with potential to become a preferred option for type 2 diabetes.

Marketed/Phase IV drugs: Under real-world post-marketing surveillance. Representative agents include orforglipron, mazdutide, HRS-7535, VX-880, UBT251, etc. Mazdutide and orforglipron are long-acting GLP-1 agonists with once-weekly dosing to improve adherence. VX-880 is an islet cell therapy providing breakthrough options for patients with advanced β-cell failure.

2.2.4. Lifestyle modifications

Lifestyle intervention [17] is the foundation of comprehensive diabetes management throughout the disease course, covering three core dimensions: Mediterranean diet, regular physical activity and family/social support. Scientific implementation is critical for glycemic control, complication prevention and quality of life.

The Mediterranean diet [18] is based on whole grains, fresh vegetables, fruits, legumes and nuts, with moderate fish and olive oil, and strict restriction of red meat, refined sugar and trans fats. Cooking methods are light (steaming, boiling, cold dressing), with controlled total calories and carbohydrates, and small frequent meals to stabilize postprandial blood glucose. Staples prioritize low-glycemic-index foods such as brown rice and oats; fats are mainly unsaturated fats such as olive oil; proteins focus on fish, shrimp, soy products and small amounts of lean meat, balancing nutrition and glycemic management.

Physical activity should be performed under stable blood glucose and without severe complications, following principles of regularity, moderation and long-term adherence. It combines aerobic exercise (main) and resistance training (auxiliary) with flexibility exercises to enhance insulin sensitivity. Aerobic exercise (brisk walking, jogging, etc.) is recommended at least 5 times

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weekly for ~30 minutes each session. Resistance training (dumbbells, resistance bands) is recommended 2–3 times weekly to increase muscle mass. Blood glucose should be monitored before and after exercise; fasting exercise is avoided to prevent hypoglycemia, and comfortable shoes and socks are worn to protect the feet.

Family and social support [19] is essential for sustained treatment adherence. Families should coordinate dietary changes, monitor medication and blood glucose, provide psychological support, and promote regular routines, smoking cessation and alcohol restriction. Socially, patients can access education and peer support through communities and lectures, and receive professional guidance via community chronic disease management and medical follow-up.

3. Function and dysfunction of pancreatic islet β-cells

3.1. Physiological function of islet β-cells

The core pathogenesis of type 2 diabetes is the synergistic interaction between insulin resistance and insufficient insulin secretion, which mutually reinforce and drive disease progression. On the basis of insulin resistance, genetic susceptibility and multiple environmental risk factors (high-fat diet, sedentary lifestyle, obesity, chronic sleep deprivation, excessive psychological stress, etc.) cooperatively induce progressive failure of islet β-cells—a key pathological event and central driver of type 2 diabetes [8]. As the only cells that synthesize and secrete insulin, islet β-cells directly determine glycemic homeostasis; their injury disrupts glucose balance and triggers a series of diabetes-related pathophysiological changes.

Before impaired glucose tolerance appears, high-risk individuals (obesity, family history of diabetes, hypertension, dyslipidemia, etc.) already develop reduced insulin sensitivity. Islet β-cells initiate a compensatory response by increasing insulin secretion quantity and rate to maintain glycemia, entering a state of compensatory hypersecretion. This compensation masks insulin resistance temporarily, but as resistance worsens, β-cell compensatory capacity gradually becomes exhausted. When compensation can no longer counteract glycemic dysregulation, blood glucose rises progressively, leading to impaired glucose tolerance. Without timely dietary and exercise interventions, this progresses to clinical diabetes with classic symptoms: polydipsia, polyphagia, polyuria and weight loss.

Notably, typical and occult β-cell dysfunction emerges in the impaired glucose tolerance stage, progressing gradually and manifesting as: loss of the early insulin secretory peak in response to glucose, failing to respond promptly to hyperglycemia; disrupted insulin secretory rhythm, especially abnormal pulsatile secretion, causing unregulated fluctuations; markedly reduced β-cell proliferation and self-repair capacity, impairing recovery from injury; elevated proinsulin/insulin ratio, indicating impaired insulin synthesis and processing, reducing secretory quality [8]; defective pulsatile insulin secretion further impairs fine glycemic control and accelerates progression from impaired glucose tolerance to clinical diabetes.

3.2. Dysfunction of islet β-cells

Islet β-cell dysfunction is the core driver of type 2 diabetes, with severity directly determining progression rate, treatment response and long-term prognosis. Chronic hyperglycemia and hyperlipidemia induce oxidative stress and excessive ROS production, damaging β-cell membrane structure and function. Sustained stimulation by inflammatory factors including tumor necrosis factor-α, interleukin-6 and C-reactive protein activates apoptotic signaling pathways in β-cells.

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Together, these factors cause β-cell injury, dedifferentiation and even apoptosis, leading to absolute or relative insulin deficiency [20]. Importantly, β-cell dysfunction precedes clinical hyperglycemia and worsens progressively with disease duration. Without targeted intervention, β-cell function becomes irreversibly damaged, increasing the risk of micro- and macrovascular complications and severely reducing quality of life.

4. Injury and death of pancreatic islet β-cells

Excessive apoptosis of β-cells is the central cause of progressive functional decline in type 2 diabetes [20]. Hyperglycemia promotes apoptosis via the Bcl-2 family, IL-1β/NF-κB and hexosamine pathways. Free fatty acids induce apoptosis through ceramide, caspase and PPAR pathways. Hyperglycemia and lipotoxicity act synergistically to exacerbate β-cell death via oxidative stress [20].

4.1. Injury of islet β-cells

4.1.1. Endoplasmic reticulum stress

Chronic glucolipotoxicity strongly activates endoplasmic reticulum (ER) stress in islet β-cells, triggering the unfolded protein response (UPR). Excessive or persistent stress activates the PERK–eIF2α–CHOP pathway and inhibits insulin synthesis and signaling via the JNK pathway, promoting apoptosis [21]. Studies in MIN6 cells and primary β-cells confirm that high glucose plus palmitic acid significantly upregulate phosphorylation of PERK and eIF2α, activating ER stress, while increasing JNK phosphorylation [21]. The JNK inhibitor SP600125 reverses IRS-1 Ser307 phosphorylation, restores insulin signaling and reduces apoptosis, indicating that the JNK–IRS-1 pathway is a key node in ER stress-mediated β-cell apoptosis [21]. Dysfunction of the ubiquitin–proteasome system and lysosomal degradation pathways further aggravate proteotoxic stress, which together with autophagic disturbance contributes to β-cell injury [22].

4.1.2. Oxidative stress

Hyperglycemia induces excessive production of ROS and reactive nitrogen species (RNS), causing oxidative damage. Nrf2 is a key antioxidant transcription factor that defends against oxidative stress by regulating antioxidant enzymes (HO-1, NQO1, etc.) [9,23,24]. P62, LC3-II, γ-H2AX, EBP-β and others participate in crosstalk between oxidative stress and autophagy [22].

Oxidative stress directly activates the NLRP3 inflammasome, promoting release of IL-1β, IL-6, MCP-1 and other inflammatory factors, forming a positive feedback loop of oxidative stress–inflammation–cell death [9]. In INS-1 cells, oxidative stress is a common upstream trigger of abnormal autophagy, mitochondrial damage, pyroptosis and ferroptosis [22]. As figure 1 shown ROS signaling pathway.

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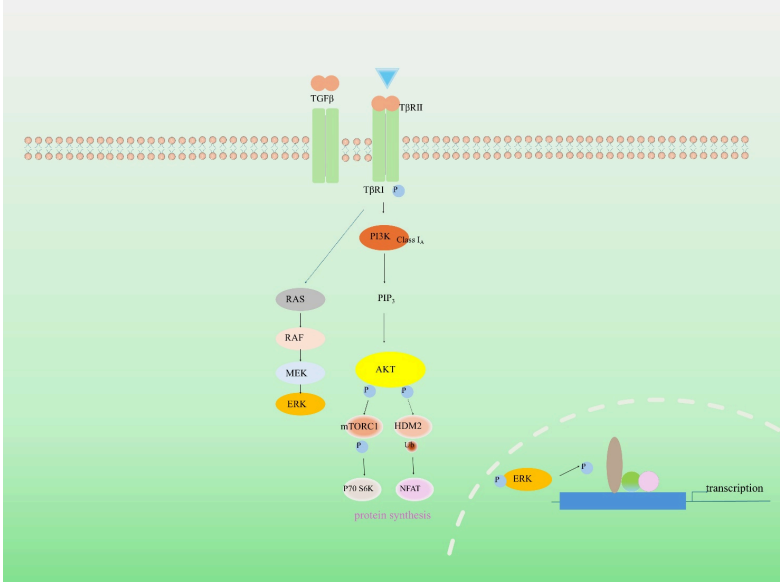


Figure 1. ROS signaling pathway

4.1.3. Mitochondrial damage

Mitochondria are central hubs for energy metabolism and ROS production, and major targets of hyperglycemic injury. Glucolipotoxicity reduces mitochondrial membrane potential, damages mtDNA, impairs respiratory chain function and decreases ATP production, limiting insulin secretion [10]. Opening of the mitochondrial permeability transition pore further initiates apoptosis. Mitochondrial dysfunction is a common convergence point for autophagy, oxidative stress, inflammation and cell death [9].

4.1.4. Lipotoxicity

Abnormal accumulation of free fatty acids (FFA) in islets causes lipotoxicity, inducing β-cell apoptosis via ceramide synthesis, ER stress, ROS elevation, mitochondrial damage and other pathways [20]. Saturated fatty acids (e.g., palmitic acid) are significantly more toxic than unsaturated fatty acids.

4.1.5. Abnormal insulin secretion

Defects include impaired glucose sensing, disrupted calcium signaling, blocked insulin granule exocytosis, loss of pulsatile secretion and abnormal proinsulin processing, collectively causing disordered insulin secretory phases and insufficient total output [8].

4.1.6. Other mechanisms

Abnormal calcium regulation, dysfunction of CPCP family proteins, epigenetic modifications (methylation, demethylation), β-cell dedifferentiation and transdifferentiation also contribute to functional decline [25,26].

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4.2. Death of islet β-cells

In recent years, multiple non-apoptotic forms of programmed cell death have been implicated in diabetes progression, including autophagy, apoptosis, pyroptosis, ferroptosis and cuproptosis, with complex crosstalk among them [26]. Pyroptosis: Inflammatory death dependent on the NLRP3–Caspase-1/11–GSDMD pathway, releasing large amounts of IL-1β and IL-18 and aggravating local inflammation and β-cell loss. Ferroptosis: Iron-dependent death characterized by lipid peroxide accumulation, glutathione depletion and System Xc^- inhibition, strongly driven by ROS. Cuproptosis: Novel copper-dependent death in which copper ions directly bind tricarboxylic acid cycle lipoylated proteins, causing abnormal protein aggregation and iron-sulfur cluster protein degradation, leading to proteotoxic death. Diabetic patients exhibit systemic copper metabolic disturbance [10]. Defective mitophagy is a common upstream event for these deaths: accumulation of damaged mitochondria, ROS burst, oxidative stress, activation of pyroptosis, ferroptosis and cuproptosis [9].

4.2.1. Autophagy in islet β-cells

Autophagy is a highly conserved homeostatic mechanism by which cells degrade damaged organelles, misfolded proteins and metabolic wastes via lysosomes, critical for β-cell survival and functional stability. Core autophagy markers include conversion of LC3-I to LC3-II, Beclin-1, Atg family proteins, P62, and regulatory pathways such as mTOR and AMPK [27]; the LC3-II/LC3-I ratio is a classic gold standard for autophagic flux. Under physiological conditions, autophagy exerts clear protective effects on β-cells: removes damaged mitochondria via mitophagy to reduce ROS generation; alleviates ER stress and metabolic pressure; maintains normal insulin synthesis and secretion; suppresses inflammation and apoptosis to reduce β-cell injury [25,26].

4.2.2. Key signaling pathways

The occurrence and regulation of islet β-cell death rely on coordinated interactions among multiple signaling pathways, which directly participate in various programmed death processes and jointly influence cell survival via crosstalk. Core pathways regulating autophagy are also involved in β-cell death, as detailed below.

mTOR pathway: A central regulator of β-cell death, with abnormal activity linked to injury. Under nutrient-sufficient conditions, mTOR activation inhibits autophagy to maintain normal metabolism. Chronic glucolipotoxicity causes excessive mTOR activation, persistently suppressing autophagy and preventing clearance of damaged components, inducing injury and death [27]. Excessive mTOR also indirectly promotes pyroptosis and ferroptosis, exacerbating β-cell loss.

AMPK pathway: An energy-sensing pathway with protective roles. Activated under energy stress (low glucose, hypoxia), AMPK inhibits mTOR to restore autophagy, clears damaged organelles, maintains homeostasis and reduces death. It also directly regulates death-related genes and suppresses oxidative injury, protecting β-cells from glucolipotoxicity [11].

JNK pathway: Participates in β-cell death via multiple mechanisms. It phosphorylates the autophagy protein Beclin-1 to modulate autophagic activity. Activated by glucolipotoxicity and oxidative stress, JNK promotes apoptosis and pyroptosis directly and via autophagic disturbance. It also mediates β-cell protection by metformin through regulating autophagy and death signaling [28].

PINK1/Parkin pathway: Mainly regulates β-cell death via mitophagy, essential for homeostasis. It specifically recognizes and eliminates damaged mitochondria to preserve function, preventing ROS

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bursts and oxidative stress that trigger pyroptosis, ferroptosis and cuproptosis [9]. Dysfunction causes mitophagy defects, a common upstream driver of multiple death modes accelerating β-cell loss.

Beyond these pathways, disrupted autophagic balance is a key regulator of β-cell death, closely linked to signaling cascades. Autophagy in β-cells is dose-dependent: moderate activation protects cells by clearing damage and relieving metabolic stress; insufficient or excessive autophagy disrupts homeostasis, causing injury and death. Glucolipotoxicity dysregulates autophagy via FTO-mediated m6A demethylation, leading to abnormal activation and exacerbating injury, while modulating the above pathways to promote death in type 2 diabetes [22].

Notably, β-cell autophagy is strictly dose-dependent: moderate activation effectively preserves function; insufficient or excessive autophagy causes injury and accelerates death. Glucolipotoxicity dysregulates autophagy via FTO-mediated m6A demethylation, triggering abnormal activation and worsening injury in type 2 diabetes pathogenesis [22].

5. Conclusion

Progressive injury and death of islet β-cells are central to the development and progression of diabetes. Hyperglycemia and lipotoxicity induce ER stress, oxidative stress and mitochondrial dysfunction, which in turn activate multiple programmed deaths including apoptosis, pyroptosis, ferroptosis and cuproptosis, accompanied by release of inflammatory factors such as IL-1β and IL-6, forming a chronic inflammatory amplification loop.

Mitophagy plays a key protective role in maintaining β-cell homeostasis, and its dysfunction is a common trigger for various cell deaths. These death modes do not act independently but form a complex interactive regulatory network through ROS, inflammasomes, JNK, AMPK/mTOR and other pathways. This review systematically summarizes the mechanisms of mitophagy, pyroptosis, ferroptosis, cuproptosis and inflammatory factors in diabetes, providing new insights and theoretical support for early intervention and targeted drug development for diabetes.

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