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Research Progress on Biological Mechanisms of Type 2 Diabetes Mellitus

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Abstract. Type 2 diabetes mellitus (T2DM) is a globally prevalent chronic metabolic disease, pathologically characterized by insulin resistance and progressive functional deterioration of pancreatic β-cells. Its pathogenesis involves synergistic regulation of multiple systems and signaling pathways. With the rapid development of molecular biology and cell biology technologies in recent years, the research on biological mechanisms of T2DM has been continuously deepened. Accumulated studies have confirmed that abnormal insulin signaling, chronic low-grade inflammation, oxidative stress and mitochondrial dysfunction, glucolipotoxicity, gut microbiota dysbiosis, and dysregulated cell death patterns are closely involved in the occurrence and progression of T2DM. This paper systematically reviews the research progress on core biological mechanisms of T2DM, integrates key links including insulin signaling pathway, pancreatic β-cell injury, inflammation-oxidative stress loop, and gut microbiota regulation. Meanwhile, the prospect of targeted therapeutic strategies based on biological mechanisms is discussed, aiming to provide comprehensive theoretical references for precise prevention, early diagnosis and innovative drug development of T2DM.

Keywords: Type 2 diabetes mellitus, cell ultrastructure, cellular inflammation, cell death, insulin resistance

1. Introduction

Diabetes mellitus is a common metabolic disorder characterized by persistent hyperglycemia, which is mainly divided into type 1 and type 2 diabetes, among which type 2 diabetes has a higher prevalence and greater global health impact [1]. Diabetes has become a worldwide public health concern. Statistics showed that approximately 537 million adults suffered from diabetes globally in 2021, and the number is projected to reach 1.31 billion by 2025 [2]. Long-term hyperglycemia induces multiple microvascular and macrovascular complications, including diabetic retinopathy, cardiovascular and cerebrovascular diseases, and diabetic foot lesions. In severe cases, patients may face irreversible consequences such as amputation and blindness, seriously impairing quality of life [1].

Furthermore, epidemiological studies have demonstrated that diabetic patients have a higher risk of mental disorders than the general population. Depression and anxiety can accelerate the deterioration of diabetic conditions, while chronic hyperglycemia and metabolic disturbance in turn

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aggravate depressive symptoms, forming a vicious cycle between metabolic and mental disorders [3, 4]. Therefore, in-depth exploration of the pathogenesis of T2DM is essential for its prevention and clinical intervention.

Unlike type 1 diabetes characterized by absolute insulin deficiency, T2DM is manifested as relative insulin insufficiency dominated by insulin resistance [5]. Insulin resistance is closely associated with structural and functional defects in the insulin signaling cascade [6]. Currently, pharmacological intervention remains the main clinical treatment for T2DM, including metformin, sulfonylureas, exogenous insulin and other hypoglycemic agents [7].

In addition, cellular inflammation is tightly correlated with T2DM pathogenesis. Excessive secretion of pro-inflammatory cytokines such as TNF-α interferes with insulin signaling transduction, induces insulin resistance and promotes the onset of T2DM [8]. Cytokines represented by TNF-α also trigger pancreatic β-cell apoptosis via the NF-κB signaling pathway, leading to β-cell damage and facilitating the progression of diabetic complications such as diabetic nephropathy [9, 10]. Persistent hyperglycemia induces excessive reactive oxygen species (ROS) accumulation and triggers oxidative stress [10]. Oxidative stress further activates NF-κB and upregulates the transcription of pro-inflammatory cytokines including TNF-α, forming a positive feedback loop between oxidative stress and inflammation [11]. Moreover, ROS overaccumulation causes mitochondrial dysfunction, and impaired mitochondria in turn produce more ROS, exacerbating intracellular oxidative damage and metabolic disturbance [12]. This paper systematically elaborates the core pathogenesis and latest research progress of T2DM from multiple molecular and cellular perspectives.

2. Pathogenesis of T2DM

T2DM is a complex multifactorial disease driven by the combined effects of genetic susceptibility, environmental factors, metabolic disorder and immune abnormality. Its core pathogenesis revolves around two key links: impaired insulin action and insufficient insulin secretion, involving functional disorders of multiple organs including adipose tissue, liver, skeletal muscle, pancreatic islets and intestine. Various pathological mechanisms interact and mutually promote each other, jointly driving the initiation and progression of T2DM.

2.1. Insulin signaling transduction pathway

The insulin signaling transduction pathway is a core signaling network regulating glucose metabolism and maintaining blood glucose homeostasis, as well as a key therapeutic target for T2DM pathological injury. Its physiological cascade is highly conservative and precisely regulated. Under physiological conditions, pancreatic β-cells synthesize and secrete insulin into the blood circulation in response to blood glucose fluctuation. Insulin binds to specific receptors on the surface of skeletal muscle, adipose and hepatic target cells, induces conformational changes and tyrosine autophosphorylation of the intracellular domain, and activates the tyrosine kinase activity of InsR to initiate signal transduction.

Activated InsR specifically recognizes and phosphorylates downstream insulin receptor substrate (IRS) family proteins, which is the central hub for downstream signal transmission. Phosphorylated IRS recruits and activates PI3K, which catalyzes the generation of second messenger PIP_3. PIP_3 further recruits and activates Akt to complete phosphorylation modification and acquire biological activity [5, 6].

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As a core downstream effector molecule, activated Akt phosphorylates a series of downstream substrates and initiates glucose metabolism-related biological effects. On the one hand, Akt promotes the translocation, membrane anchoring and stable expression of intracellular GLUT4, enhances cellular glucose transport capacity and accelerates glucose uptake and utilization. On the other hand, activated Akt inhibits key enzymes of hepatic gluconeogenesis, reduces endogenous glucose production and promotes glycogen synthesis. Through the above synergistic effects, the insulin signaling pathway lowers blood glucose and maintains glucose metabolic homeostasis.

In T2DM, any dysfunction in the insulin signaling pathway, including decreased InsR expression, abnormal IRS phosphorylation, blocked PI3K/Akt activity and impaired GLUT4 translocation, leads to signal interruption and efficiency decline, directly induces insulin resistance [9] and constitutes the molecular basis of T2DM pathogenesis. The signaling pathway of insulin resistance is shown in Figure 1.

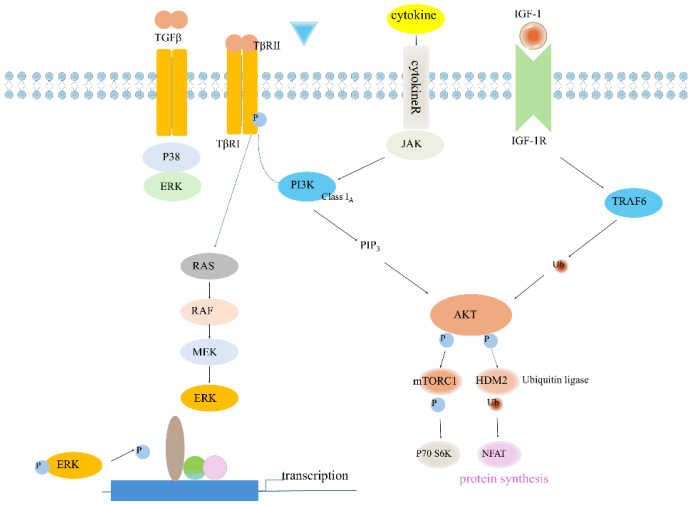

Figure 1. The signaling pathway of insulin resistance

2.2. Molecular mechanism of obesity-mediated insulin resistance

Obesity is the most crucial independent risk factor for T2DM, and central obesity is significantly positively correlated with the development of insulin resistance. Under obese conditions, excessive lipid accumulation induces functional remodeling of adipose tissue, transforming it from a simple energy-storing organ into a central hub linking immune inflammation and metabolic dysregulation.

Traditional view holds that adipose overaccumulation mechanically compresses peripheral tissues and disturbs metabolism. Accumulating modern evidence indicates that ectopic deposition of lipid intermediates is the core mechanism of obesity-induced insulin resistance. Excessive free fatty acids are ectopically deposited in skeletal muscle, liver and pancreas, generating toxic lipid intermediates such as ceramide and diacylglycerol. Ceramide directly suppresses PI3K activation and blocks Akt phosphorylation, thereby disrupting insulin signaling. Diacylglycerol activates protein kinase C (PKC) and further promotes abnormal phosphorylation of IRS proteins. Meanwhile, obese adipose tissue secretes abundant pro-inflammatory cytokines and free fatty acids, induces systemic chronic

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low-grade inflammation, and forms a pathological axis of "obesity-inflammation-insulin resistance" to accelerate T2DM progression [13].

2.3. Core mechanisms of pancreatic β-cell dysfunction

Pancreatic β-cells are the only cell type capable of insulin synthesis and secretion in humans, and their quantity and functional status directly determine insulin secretory capacity. In the early stage of T2DM, insulin resistance induces compensatory hyperinsulin secretion of β-cells. Long-term compensatory overload eventually leads to β-cell exhaustion, progressive functional decline and cell apoptosis, resulting in absolute insulin deficiency and irreversible disease progression.

2.3.1. Synergistic damage of glucotoxicity and lipotoxicity

Glucotoxicity and lipotoxicity are pivotal metabolic factors inducing β-cell injury, and they exert synergistic pathological effects. Chronic hyperglycemia downregulates the expression of GLIS3, a key transcription factor that modulates the functional proteins MafA and MafB. Reduced GLIS3 expression directly impairs insulin secretion of β-cells. Excessive deposition of free fatty acids induces lipotoxicity, further disturbs β-cell metabolism, upregulates the abnormal expression of peroxisome proliferator-activated receptor (PPAR), and inhibits insulin synthesis and secretion.

Persistent glucolipotoxicity disrupts the mitochondrial structure of β-cells and impairs ATP synthesis, while ATP is the essential energy source for insulin exocytosis. Moreover, glucolipotoxicity triggers endoplasmic reticulum stress and activates the unfolded protein response, ultimately inducing β-cell apoptosis, which accounts for the reduction of β-cell mass during T2DM progression.

2.3.2. Chronic inflammation-mediated β-cell injury

Chronic low-grade inflammation acts as a critical bridge linking insulin resistance and β-cell damage. Under metabolic stress, islet resident macrophages (IRMs) are abnormally activated, triggering the TLR4/NF-κB and cGAS-STING pathways to activate the NLRP3 inflammasome, followed by massive release of pro-inflammatory cytokines such as TNF-α and IL-1β.

On the one hand, pro-inflammatory cytokines block insulin signaling via the JNK pathway and aggravate systemic insulin resistance. On the other hand, they directly act on pancreatic β-cells, inhibit the expression of β-cell-specific transcription factors such as PDX-1 and MafA, induce β-cell dedifferentiation and loss of insulin secretory function. Meanwhile, inflammatory cytokines activate apoptotic pathways and cause massive β-cell death. Damaged β-cells further release damage-associated molecular patterns, recruit and activate more immune cells, and form a vicious cycle of "inflammation-cell injury" to accelerate β-cell functional failure.

2.3.3. Gene mutation and genetic susceptibility

Genetic predisposition is an indispensable risk factor for T2DM, and multiple gene mutations are closely associated with β-cell dysfunction. GIGYF1 is a key gene regulating β-cell survival, and loss-of-function mutation of GIGYF1 downregulates the expression of insulin-like growth factor-1 (IGF-1). IGF-1 shares high structural homology with insulin, which can promote β-cell proliferation, inhibit apoptosis and maintain cell differentiation. IGF-1 deficiency directly reduces the viability of β-cells.

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In addition, polymorphisms of TCF7L2 and KCNJ11 have been confirmed to be correlated with T2DM genetic susceptibility, which increase disease risk by regulating insulin secretion and β-cell proliferation and apoptosis.

2.3.4. Imbalanced β-cell heterogeneity, cellular senescence and transdifferentiation

Advances in single-cell RNA sequencing have revealed the critical role of β-cell heterogeneity in T2DM pathogenesis. Pancreatic β-cells consist of functionally distinct subpopulations, among which high-function subpopulations such as CD63, $CD24^{+}$ and beta1 are responsible for major insulin secretion. The proportion of these high-function subpopulations is significantly decreased in T2DM patients.

Chronic metabolic stress induces the senescence-associated secretory phenotype (SASP) of β-cells, which secretes abundant inflammatory cytokines and matrix metalloproteinases to disrupt the islet microenvironment [14]. Meanwhile, partial mature β-cells undergo transdifferentiation into α-cells or other cell types without insulin secretory function. Furthermore, epigenetic alterations such as dysregulated RNA-binding proteins and abnormal alternative splicing jointly lead to the decline in both quantity and quality of functional β-cells, driving T2DM progression.

2.4. Pathogenic mechanism of gut microbiota dysbiosis

As the largest microecological system in the human body, gut microbiota is regarded as a vital metabolic organ, and its structural and functional dysbiosis serves as an important peripheral pathogenic mechanism of T2DM. T2DM patients are characterized by decreased gut microbial diversity, reduced beneficial bacteria and enriched pathogenic bacteria.

The abundance of butyrate-producing bacteria such as Faecalibacterium and Roseburia is markedly decreased, leading to insufficient synthesis of short-chain fatty acids (SCFAs) [15]. SCFAs play crucial roles in maintaining intestinal barrier integrity, anti-inflammation and metabolic regulation. SCFA deficiency increases intestinal mucosal permeability, namely "leaky gut". Lipopolysaccharide (LPS), a component of the cell wall of Gram-negative bacteria, enters the bloodstream through the damaged intestinal barrier, induces metabolic endotoxemia, activates the TLR4/NF-κB pathway and triggers systemic chronic inflammation.

Meanwhile, abnormal accumulation of gut microbial metabolites such as branched-chain amino acids (BCAAs) and imidazole propionate activates mTORC1 and p38γ/MAPK signaling pathways respectively [16], induces abnormal phosphorylation of IRS proteins, directly blocks insulin signaling transduction and exacerbates insulin resistance. In addition, gut microbiota modulates host glucose and lipid metabolism via bile acid metabolism and neurotransmitter secretion, thereby participating in the occurrence and development of T2DM.

2.5. Oxidative stress, mitochondrial dysfunction and cell death

Hyperglycemia and hyperlipidemia-induced oxidative stress and mitochondrial dysfunction constitute the core cytological basis of T2DM cell injury [17]. They form a mutually promotional vicious cycle, and ultimately cause pancreatic β-cell exhaustion and peripheral organ damage through multiple abnormal programmed cell death patterns, which are the key driving factors for T2DM progression and diabetic complications [18].

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2.5.1. Occurrence and pathological damage of oxidative stress

Under the pathological state of T2DM, long-term metabolic stress induced by hyperglycemia and hyperlipidemia disrupts the mitochondrial respiratory chain function, leading to excessive generation of reactive oxygen species (ROS) [19]. Excess ROS surpasses the scavenging capacity of the antioxidant system, breaks the redox homeostasis and induces systemic oxidative stress. ROS mainly includes superoxide anion, hydrogen peroxide and hydroxyl radical, which possess strong oxidative activity and directly attack intracellular biological macromolecules such as proteins, lipids and DNA, triggering lipid peroxidation, protein denaturation and DNA strand breakage, and causing irreversible damage to cell structure and function.

Moreover, persistent hyperglycemia promotes massive synthesis and accumulation of advanced glycation end products (AGEs) [17]. The binding of AGEs to its receptor RAGE further activates NADPH oxidase, continuously induces ROS generation and amplifies oxidative stress. Oxidative stress not only directly impairs cellular function, but also acts as an upstream signal to activate NF-κB [20] and JNK inflammatory pathways, promotes the release of pro-inflammatory cytokines such as TNF-α and IL-1β, and forms a positive feedback loop between oxidative stress and chronic inflammation. This loop aggravates insulin resistance and pancreatic β-cell injury, acting as a critical intermediate linking metabolic disorder, inflammation and cell death.

2.5.2. Core characteristics of mitochondrial dysfunction

Mitochondria are the central organelles for cellular energy metabolism and the major source of ROS. Their structural integrity and functional normalcy are essential for maintaining cell survival. In T2DM, persistent oxidative stress and glucolipotoxicity directly induce mitochondrial structural damage and functional disorder, manifested as mitochondrial swelling, cristae fracture, decreased membrane potential, and mtDNA mutation and deletion.

Functionally, the activity of mitochondrial respiratory chain complexes is reduced and ATP synthesis is impaired, resulting in insufficient energy supply for key biological processes such as insulin secretion and glucose uptake. Meanwhile, abnormal opening of mitochondrial permeability transition pore (mPTP) releases cytochrome C and apoptosis-inducing factor (AIF) to initiate cell death programs. More importantly, damaged mitochondria fail to clear ROS normally but continuously produce more free radicals, forming a vicious cycle of "ROS accumulation → mitochondrial damage → further ROS overproduction", which further exacerbates cellular oxidative injury and functional failure. This pathological process is particularly prominent in pancreatic β-cells, skeletal muscle cells, cardiomyocytes and renal tubular epithelial cells.

2.5.3. Major cell death patterns associated with T2DM

Cell death is the ultimate execution link leading to reduced pancreatic β-cell mass and peripheral organ functional damage in T2DM [21]. In addition to classical apoptosis, emerging programmed cell death including pyroptosis, necroptosis and autophagic cell death have been confirmed to be involved in T2DM pathogenesis [22]. Different cell death patterns cross-regulate and synergize with each other, collectively driving cell exhaustion and tissue injury.

Apoptosis is the most classical and predominant death pattern leading to pancreatic β-cell loss in T2DM, which is a programmed and non-inflammatory cell death. Stimulated by glucolipotoxicity, oxidative stress and chronic inflammation, the mitochondrial apoptotic pathway is activated. Cytochrome C is released into the cytoplasm and binds to Apaf-1, triggering the caspase-9/caspase-3

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cascade reaction, followed by nuclear pyknosis, apoptotic body formation and orderly cell death [23].

Studies have verified that pro-inflammatory cytokine TNF-α activates caspase-8 via the death receptor pathway to directly induce β-cell apoptosis. Abnormal IRS phosphorylation and inhibited Akt signaling further weaken cell survival signals and accelerate apoptotic progression. Persistent apoptosis of pancreatic β-cells directly reduces the number of insulin-secreting cells and causes insufficient insulin secretion, marking the transition of T2DM from compensatory stage to decompensatory stage.

Pyroptosis is an inflammatory programmed cell death mediated by inflammasome, serving as a key link connecting metabolic stress, chronic inflammation and cell death. In T2DM [23], hyperglycemia, hyperlipidemia and ROS accumulation activate the NLRP3 inflammasome in pancreatic islets and peripheral tissues, which further cleaves and activates caspase-1/4/5 and cuts Gasdermin D (GSDMD). Cleaved GSDMD induces plasma membrane perforation and cell swelling rupture, accompanied by massive release of pro-inflammatory factors IL-1β and IL-18.

Distinct from apoptosis, pyroptosis is accompanied by intense inflammatory response. The released inflammatory factors further recruit and activate macrophages and other immune cells, amplify local inflammation, and form a vicious cycle of "inflammation-pyroptosis-exacerbated inflammation". Pyroptosis not only accelerates pancreatic β-cell death, but also aggravates inflammatory injury in liver, skeletal muscle and kidney, serving as a core mechanism underlying diabetic nephropathy, diabetic cardiomyopathy and other complications.

Necroptosis is a regulated form of necrosis that predominates when caspase activity is inhibited, characterized by plasma membrane rupture, intracellular substance leakage and intense inflammatory activation. Inflammatory cytokines such as TNF-α activate the RIPK1/RIPK3/MLKL [24] necroptotic signaling axis. Oligomerized MLKL inserts into the plasma membrane, destroys membrane integrity and induces sterile inflammation due to intracellular content release [23].

In T2DM, necroptosis mainly participates in the destruction of islet microenvironment and peripheral tissue injury. Excessive activation of necroptosis aggravates insulin resistance and accelerates necrotic loss of β-cells, which synergizes with apoptosis and pyroptosis to reduce β-cell mass.

Autophagy is a cellular self-protective mechanism that degrades damaged organelles and misfolded proteins via lysosomes to maintain intracellular homeostasis. Moderate autophagy eliminates damaged mitochondria, reduces ROS generation and preserves β-cell function. However, under long-term metabolic stress of T2DM, excessive activation or blockage of autophagic flux leads to autophagy dysfunction and subsequent autophagic cell death.

Oxidative stress and mitochondrial damage excessively activate autophagy, resulting in excessive degradation of cytoplasmic components and organelles beyond cellular repair capacity, and eventually inducing autophagic cell death. By contrast, autophagy deficiency leads to accumulation of damaged mitochondria and overproduction of ROS, further exacerbating apoptosis and pyroptosis. Therefore, disrupted autophagy homeostasis is an important auxiliary mechanism for functional decline and death of pancreatic β-cells.

2.5.4. Integral role of abnormal cell death in T2DM

In the occurrence and progression of T2DM, oxidative stress and mitochondrial dysfunction act as upstream core inducers, while multiple cell death patterns serve as downstream execution links to mediate pathological injury. In pancreatic islets, apoptosis, pyroptosis and necroptosis synergistically reduce functional β-cell mass and cause insufficient insulin secretion. In peripheral

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tissues, death of skeletal muscle and adipocytes aggravates insulin resistance, while hepatocyte death disturbs glucose and lipid metabolism. In complication-related organs, abnormal death of renal, retinal and cardiovascular cells directly mediates the occurrence and development of chronic diabetic complications.

3. Conclusion

Based on the biological mechanisms of T2DM, novel therapeutic strategies have shifted from simple hypoglycemic control to targeted pathway intervention, β-cell protection and insulin resistance reversal. Targeted regulation of the PI3K/Akt insulin signaling pathway can effectively improve insulin sensitivity of target organs. Anti-inflammatory intervention targeting NLRP3 inflammasome and TNF-α blocks inflammation-mediated cellular injury. Mitochondria-targeted antioxidants alleviate oxidative stress and mitochondrial dysfunction. Gut microbiota regulators such as probiotics, prebiotics and fecal microbiota transplantation restore intestinal microecological balance and improve metabolic disorder. In addition, cutting-edge technologies including β-cell heterogeneity-based cell replacement therapy and gene therapy provide novel directions for reversing β-cell functional failure.

Future research should further integrate multi-omics technologies to dissect the interactive network among various T2DM mechanisms, and develop precise, safe and efficient targeted drugs, so as to realize early intervention and precise treatment of T2DM. The pathogenesis of T2DM is a complex interactive network involving multiple factors, pathways and organs. Insulin resistance serves as the core initiating link, and progressive pancreatic β-cell functional decline acts as the key marker of disease progression. Chronic inflammation, oxidative stress, mitochondrial dysfunction, gut microbiota dysbiosis, glucolipotoxicity and dysregulated cell death interact and mutually promote each other, forming an integrated pathological system. With the in-depth exploration of T2DM biological mechanisms, the understanding of T2DM has extended from clinical symptoms to molecular, cellular and organ levels, laying a solid foundation for the discovery of novel therapeutic targets and formulation of intervention strategies. Further exploration of the cross-regulatory network among pathological mechanisms will facilitate the development of precise targeted therapies and provide new insights for the prevention and treatment of T2DM.

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