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# *Research Progress of Pancreatic β-Cell Autophagy in Diabetes*

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***Abstract.*** Persistent hyperglycemia impairs insulin secretory responses and reduces insulin-mediated glucose transport. Long-term and sustained hyperglycemia in the body can induce irreversible damage or even death of β-cells. Autophagy of pancreatic islet cells exerts a positive regulatory effect in the treatment of diabetes. β-Cell autophagy can activate associated macrophages and inhibit T cell-mediated autoimmune responses. The key proteins regulating β-cell autophagy include LC3-I, LC3-II, P53, PI3K etc., and the critical signaling pathways involve the mTOR pathway, AMPK pathway, JNK pathway and other cascades. This review summarizes the influencing factors of β-cell autophagy and its latest research progress in a diabetes-related environment.

***Keywords:*** β-cell, Autophagy, Autoimmune response, Diabetes mellitus

## 1. Introduction

### 1.1. Epidemiology and clinical significance of diabetes

In the 21st century, diabetes mellitus (DM) ranks among the global health challenges with the most rapid development [1]. According to the 11th edition of the IDF Diabetes Atlas, the global number of adults aged 20–79 years diagnosed with diabetes reached 589 million in 2024, among whom more than 9.5 million suffered from type 1 diabetes (T1DM); the total number of patients is projected to reach 853 million by 2050. The prevalence of gestational diabetes mellitus (GDM) has been on a continuous rise, and up to 43% of diabetes patients (predominantly type 2 diabetes) remain undiagnosed [2]. T1DM arises from the autoimmune-mediated destruction of pancreatic β-cells, which results in absolute insulin deficiency [3]; while most frequently diagnosed in children and adolescents, T1DM may develop at any stage of life [4], and affected patients are dependent on exogenous insulin for survival [5]. Among the globally diagnosed T1DM patients, 22.3% live in low-income countries, predominantly in the 20–59 years age group, with the highest number of cases recorded in the European region. Type 2 diabetes mellitus (T2DM) constitutes more than 90% of all diabetes cases globally, characterized by the presence of insulin resistance that progresses to β-cell functional failure with disease advancement [6]. Its clinical manifestations are often insidious, and it is closely associated with overweight, advanced age, ethnicity and family history, with a markedly increased prevalence in adults under 40 years old and obese children and adolescents.

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### 1.2. Pathogenesis of diabetes

As a frequent chronic autoimmune disease, T1DM is attributed to the interplay of genetic, immunological and environmental factors. Immune-mediated pancreatic β-cell destruction, particularly islet inflammation involving T lymphocytes, results in irreversible insulin deficiency, and patients require lifelong insulin replacement therapy [7]. T2DM, a chronic metabolic condition, is defined by impaired insulin utilization and reduced insulin effectiveness [8], with core features of persistent hyperglycemia, insulin resistance and relative insulin deficiency [9]. T2DM is a major contributing factor to the development of cardiovascular and cerebrovascular diseases, such as atherosclerotic heart disease and myocardial infarction [10], and it also significantly elevates the risk of stroke, with cardiovascular complications being the leading cause of death in T2DM patients [11].

### 1.3. Therapeutic approaches for diabetes

Pharmacotherapy is currently the most effective clinical intervention for DM. Antidiabetic drugs are mainly classified into two categories: chemical drugs and biological agents [12]. Although all these agents can lower blood glucose to a certain extent, they differ significantly in their mechanisms of action, clinical applicability for different patient populations and adverse effect profiles. In-depth investigations into the pathogenesis of diabetes should be continuously strengthened to develop more personalized therapeutic strategies for diabetic patients [13].

#### 1.3.1. Chemical drugs

Chemical antidiabetic agents include sulfonylureas, meglitinides, thiazolidinediones, biguanides and α-glucosidase inhibitors [14]. Sulfonylureas and meglitinides exert hypoglycemic effects by promoting insulin secretion; thiazolidinediones reduce insulin resistance, inhibit hepatic gluconeogenesis and improve peripheral glucose utilization; biguanides and α-glucosidase inhibitors lower blood glucose by reducing intestinal glucose absorption, inhibiting hepatic gluconeogenesis and delaying carbohydrate metabolism. Despite their definite hypoglycemic efficacy, these chemical drugs have notable limitations and adverse effects. The main limitations include contraindications in patients with renal insufficiency, heart failure and post-operative status, leading to delayed or ineffective treatment in these populations. The major adverse effects include hypoglycemia, weight gain, gastrointestinal reactions, anemia and potential carcinogenicity [14-15].

#### 1.3.2. Biological drugs

Biological antidiabetic agents include insulin and its analogs, GLP-1 receptor agonists, SGLT2 inhibitors and amylin analogs [14]. Insulin plays an indispensable role in diabetes treatment [16]: animal insulin has strong immunogenicity and is prone to induce allergic reactions and lipoatrophy, while human insulin exhibits significantly reduced immunogenicity, and insulin analogs have unique advantages in simulating physiological insulin secretion patterns. GLP-1 receptor agonists achieve pharmacological concentrations via exogenous supplementation of GLP-1, with a prominent hypoglycemic effect that reduces HbA1c by approximately 0.8~1.5% [17]. SGLT2 inhibitors lower the renal glucose threshold, exert their effects by targeting SGLT2 to inhibit renal glucose reabsorption and facilitate urinary glucose excretion. Amylin analogs can delay glucose absorption, inhibit glucagon secretion, reduce hepatic gluconeogenesis, slow gastric emptying and increase satiety, and thus serve as an adjuvant therapy for both T1DM and T2DM [14].

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### 1.3.3. Investigational drugs

Conventional antidiabetic drugs suffer from drawbacks such as unsustained efficacy, numerous adverse effects and easy induction of insulin resistance [18,19], highlighting an urgent need for more effective and safe novel agents. Current investigational antidiabetic drugs include novel SGLT2 inhibitors, GLP-1 receptor agonists and GK activators. Acidic fibroblast growth factor (FGF1) and its derivatives exert a rapid effect in restoring normoglycemia in T2DM mice, exert insulin-sensitizing effects and avoid the development of insulin resistance. Compared with clinical hypoglycemic drugs, FGF1 has a longer duration of action and higher safety, with a specific hypoglycemic effect in the treatment of T2DM [20]. However, research on its underlying mechanism is still in the early stage, and most relevant data are derived from animal experiments; thus, verification of interspecies differences is required before clinical translation [21]. Phase I clinical study of the SGLT2 inhibitor rongliflozin demonstrated similar PK/PD profiles and good tolerability in healthy subjects and T2DM patients [22-25]. Clinical trials PF-06882961 of GLP-1 receptor agonists in Phase II showed that the drug effectively reduces body weight and plasma glucose with favorable safety and PK/PD characteristics, supporting its further clinical development [26,27]. A Phase III clinical trial of the GK activator PB201 is currently underway in Chinese T2DM patients to evaluate its efficacy and safety [28]

## 2. Pancreatic β-cell function

The synthesis, storage, and pulsatile release of insulin-key processes for maintaining blood glucose homeostasis—constitute the core functions of β-cells [29-30]; In addition, β-cells secrete a variety of hormones and peptide factors. When blood glucose elevates, glucose enters β-cells via glucose transporters, is phosphorylated by glucokinase and then enters metabolic pathways, leading to an increased ATP/ADP ratio. This ratio change closes ATP-modulated $K^+$ channels and triggers membrane depolarization, leading to the activation of voltage-gated calcium channels. The influx of $Ca^{2+}$ ultimately induces the release of insulin via vesicle exocytosis. This process consists of the first-phase rapid secretion and the second-phase sustained release, and is precisely regulated by hormonal and neural signals. Pancreatic β-cells also possess self-regulatory capacity and can maintain their quantity and functional integrity through division and proliferation under physiological conditions.

## 3. Pancreatic β-cell dysfunction

Early manifestations of β-cell dysfunction include abnormal insulin secretion and decreased glucose sensitivity. Glucolipotoxicity, blood glucose fluctuations, chronic non-specific inflammatory responses induced by environmental endocrine-disrupting chemicals, oxidative stress, endoplasmic reticulum stress (ERS) and mitochondrial functional impairment are key factors resulting in the decline of insulin secretory capacity and cellular senescence of pancreatic β-cells [31-33]. In addition, multiple genes including Pax6, TCF7L2, CDKAL1, SLC30A8 and HHEX are correlated with β-cells dysfunction. Among them, Pax6 [34] and HHEX [35], as key transcription factors, regulate the lineage differentiation and proliferative capacity of islet cells respectively, and are crucial for retaining β-cell identity and maintaining its functional reserve; TCF7L2 [36] mediates β-cell proliferation and glucose-stimulated insulin secretion—specifically the first-phase secretion—by means of the Wnt signaling pathway. In the insulin secretory process, CDKAL1 [37] interferes with the conversion efficiency of proinsulin to mature insulin by affecting tRNA modification,

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which is prone to induce ERS; the zinc transporter encoded by SLC30A8 [38] is responsible for transporting zinc ions into insulin vesicles to ensure the stable storage and secretion of insulin. Risk variants of these genes usually do not cause disease independently, but their cumulative minor effects lead to gradual functional decline, dedifferentiation and even apoptosis of β-cells under metabolic stress, thus significantly impairing the compensatory capacity of insulin secretion.

## 4. Pancreatic β-cell injury and death

The main modes of pancreatic β-cell injury include apoptosis, necrosis, pyroptosis and ferroptosis, with underlying mechanisms involving metabolic stress, impaired insulin secretion regulation, alterations in the islet microenvironment and cellular dedifferentiation [39-43]. Inflammatory factors can inhibit the insulin signaling pathway, leading to decreased insulin sensitivity, β-cell apoptosis, pyroptosis and functional impairment [44], with IL-1β being the key mediator [43] (see Figure 1: JNK signaling pathway). Studies have also found that damaged β-cells under high-fat and high-glucose stimulation can produce mature IL-1β through cellular reprogramming, thereby inducing their own apoptosis [45]. In T1DM, β-cell loss serves as the core driving factor for disease development: autoimmune responses induce massive, irreversible destruction of β-cells, which results in absolute insulin deficiency, making patients dependent on exogenous insulin for survival. The exact death mechanism of β-cells in T1DM remains unclear, but apoptosis is considered the major death mode in the early stage of the disease [46]. In T2DM, β-cell loss is characterized by progressive functional decline and a mild reduction in cell quantity: the disease is initially dominated by insulin resistance, and under the action of glucolipotoxicity, oxidative stress and other factors, β-cells exhibit accelerated apoptosis and dedifferentiation [43], but the reduction in cell quantity is usually less severe than that in T1DM, and residual β-cells still retain partial secretory function. Therefore, β-cell loss is the direct cause of T1DM onset, and a critical link in the progression and deterioration of T2DM.

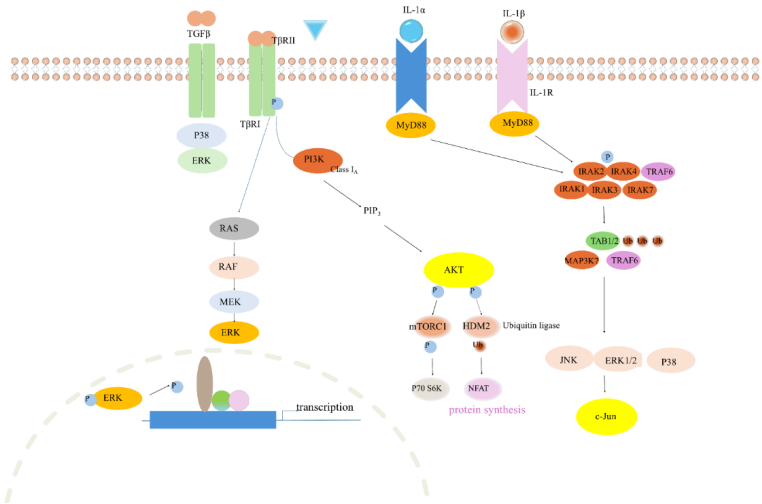



Figure 1. JNK signaling pathway

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## 5. Pancreatic β-cell autophagy

### 5.1. Basic concepts and detection markers of autophagy

Autophagy represents a lysosome-dependent degradative process exclusive to eukaryotic cells, responsible for the breakdown of cytoplasmic components including misfolded proteins, damaged organelles, and pathogenic invaders to support cellular homeostasis. Based on the differences in substrates and their delivery routes to lysosomes, autophagy is primarily divided into three categories: chaperone-mediated autophagy, microautophagy and microautophagy [47]. Autophagy is a highly conserved cellular process that can alleviate the damage of inflammation, oxidative stress and ERS to β-cell function and delay the progression of diabetes. Three sequential stages constitute the autophagic process: initiation-nucleation, elongation-completion, and degradation-recovery [48]. During the initiation step of autophagy, mTORC1 is inactivated under starvation conditions, releasing the ULK1 complex; ULK1 then phosphorylates Beclin 1, which forms a complex with Atg14L, Vps15 and Vps34 to generate PI3P, thereby recruiting downstream proteins to initiate autophagosome nucleation. The conversion of LC3-I to LC3-II occurs in the elongation stage: Atg7 (E1-like enzyme) and Atg3 (E2-like enzyme) mediate the conjugation of LC3-I to phosphatidylethanolamine (PE) to form lipidated LC3-II, a process promoted by the Atg12-Atg5-Atg16L1 complex (E3-like enzyme). LC3-II is localized on both the inner and outer membranes of autophagosomes and serves as a key marker of autophagosome formation [49]. Following this, autophagosomes fuse with lysosomes to form autolysosomes, and the luminal contents are degraded and recycled, thereby completing the autophagic cycle.

### 5.2. The role of autophagy in maintaining the structure and function of pancreatic β-cells

In the maintenance of pancreatic β-cell structure, autophagy decreases the accumulation of islet amyloid polypeptide (IAPP) in β-cells, thereby alleviating β-cell damage and offering amino acids for endogenous peptide production [50]. Kim J et al [51]. constructed a pancreatic β-cell-specific autophagy-deficient mouse model with human IAPP (hIAPP) expression and found that these mice exhibited significant accumulation of hIAPP oligomers and amyloid in islets, increased β-cell apoptosis and a marked tendency to develop diabetes; however, this pathological tendency was not observed in mice with only hIAPP expression or only autophagy deficiency. These results confirm that autophagy can mitigate hIAPP aggregation in β-cells and thus exert a protective effect on pancreatic β-cells. In terms of maintaining pancreatic autophagy, β-cell function protects β-cells by clearing damaged mitochondria, misfolded proteins and other cytotoxic substances. Excessive sugar intake induces oxidative stress in INS-1 cells [52], which in turn triggers autophagy to alleviate cellular oxidative damage. In T2DM patients with excessive sugar intake, the high-glucose microenvironment stimulates pancreatic β-cells to secrete more insulin, which consumes a large amount of ATP and increases the metabolic burden of mitochondria. In addition, reactive oxygen species (ROS) generated in the high-glucose environment can cause severe mitochondrial damage [53,54]. Aoyagi K et al. constructed a high-fat diet (HFD)-fed autophagy-deficient mouse model and found that upregulation of autophagy significantly reduced mitochondrial damage in pancreatic β-cells of these mice [51]. These findings indicate that autophagy is essential for maintaining the cellular homeostasis of pancreatic β-cells.

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### 5.3. Regulation of β-cell autophagy by key signaling pathways

The major signaling pathways regulating β-cell autophagy include the mTOR pathway, AMPK pathway and JNK pathway. As an important protein kinase, adenosine monophosphate-activated protein kinase (AMPK) is widely expressed in living organisms. As a cellular energy sensor, AMPK regulates mitochondrial function and maintains intracellular energy homeostasis by sensing the intracellular AMP/ATP ratio [55]. In addition, AMPK plays a crucial role in mitochondrial biogenesis, cellular autophagy and mitophagy [56]. Mammalian target of rapamycin (mTOR) is a central molecule that negatively regulates autophagy; mTOR maintains organismal homeostasis by participating in a variety of biological processes, including promoting cell differentiation and proliferation, regulating mitochondrial function, enhancing intracellular anabolism and inhibiting autophagy [57]. Thus, the AMPK/mTOR signaling pathway serves as both a key node in the intracellular energy metabolism surveillance system and a crucial upstream signaling pathway governing autophagy [58]. The accumulation of hIAPP in pancreatic β-cells of T2DM patients is closely associated with the reduction in β-cell quantity and functional impairment [59]. c-Jun N-terminal kinase (JNK) modulates the expression of Beclin-1, a key protein involved in pancreatic β-cell autophagy, thereby interfering with insulin biosynthesis [60]; thus, the JNK/Beclin-1 axis plays an important regulatory role in pancreatic β-cell autophagy and functional dysfunction.

### 5.4. Effects of inflammation and stress on β-cell autophagy

#### 5.4.1. Oxidative stress

Oxidative stress refers to a series of cellular pathological reactions caused by excessive production of reactive oxygen species (ROS) that exceeds the body's antioxidant scavenging capacity, leading to an imbalance between oxidative and antioxidant processes in the body, which is a major cause of cellular injury. Hypoxia, inflammation, and high-glucose and high-fat stimulation can all induce massive ROS production; excessive ROS can cause mitochondrial dysfunction, leading to pancreatic β-cell functional impairment and structural damage. Under hypoxic conditions, autophagy can protect pancreatic β-cells by clearing oxidatively damaged proteins and organelles through its cellular defense mechanism [61]. Kaniuk NA et al. [62] found that the accumulation of ubiquitinated protein aggregates in pancreatic β-cells of obese rats can stimulate autophagy activation. Hartley T. et al. [63] confirmed that oxidative stress can induce autophagy, and autophagy can in turn inhibit oxidative stress-induced cellular injury. Clinical and basic studies have shown that mild chronic inflammation exists in the islets of obese individuals and T2DM patients, with significantly increased levels of inflammatory factors such as IL-1β, IL-6, TNF-α and IFN-γ in the islet microenvironment [64,65]. IL-1β and IFN-γ can inhibit mTOR activity and induce autophagy through the AMPK-ULK1 axis in an ERS-dependent manner mediated by endoplasmic reticulum calcium release [66]. The inflammatory mediator IL-6 can regulate autophagy to protect β-cells from apoptotic death [67,68]; furthermore, IL-6 is able to activate STAT3 and GABAA receptor 1 to further enhance autophagy in pancreatic β-cells [66].

#### 5.4.2. Endoplasmic Reticulum Stress (ERS)

As the only cells in the body capable of producing and secreting insulin, pancreatic β-cells play an irreplaceable role. When insulin resistance occurs in T2DM patients, the demand for insulin synthesis and secretion by β-cells increases significantly, which easily leads to the accumulation of

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misfolded proteins in the endoplasmic reticulum and thus induces ERS [69], ultimately resulting in insufficient insulin production or abnormal secretion [70]. Chen YY et al. [71] treated MIN6 cells with palmitate and found that palmitate can activate ERS and its downstream stress-activated protein kinase pathway to induce autophagy in pancreatic β-cells, thereby protecting the cells from ERS-induced injury. This result indicates that autophagy serves as a cellular adaptive defense mechanism to protect β-cells from ERS-induced damage. In addition, recent studies have found that the GPCR family, calcium-dependent phospholipase A2 and glycated albumin can also regulate β-cell function by modulating autophagy activity [72].

## 6. Conclusion

Autophagy exerts a bidirectional regulatory effect on pancreatic β-cells: physiological basal autophagy alleviates ERS and oxidative stress by clearing damaged organelles and toxic protein aggregates (e.g., hIAPP), thereby maintaining β-cell structure and functional homeostasis; in contrast, excessive autophagy can induce programmed cell death and accelerate the loss of β-cell function. Targeting autophagy-related signaling pathways such as AMPK/mTOR and JNK/Beclin-1 provides novel therapeutic strategies for diabetes treatment, but this approach faces multiple challenges including difficulty in tissue-specific regulation, complex dynamic monitoring of autophagic activity and potential off-target effects. Future research should focus on the development of β-cell-specific autophagy modulators, clarifying the interaction mechanism between autophagy and the islet immune microenvironment, and exploring combined intervention regimens of autophagy regulation and existing hypoglycemic drugs to improve the clinical efficacy and safety of diabetes treatment.

## References

[1] Maganioti, A.E., Chrissanthi, H.D., Charalabos, P.C., Andreas, R.D., George, P.N. and Christos, C.N. (2010) Cointegration of Event-Related Potential (ERP) Signals in Experiments with Different Electromagnetic Field (EMF) Conditions. Health, 2, 400-406.
[2] Hu Shanlian, Liu Guoen, Xu Zhangrong, Li Dakui & Hu Yonghua. (2008). Research status of diabetes epidemiology and economic burden of diabetes in China. China Health Economics, (08), 5-8.
[3] Care & Shang Lixin. (2015). Current status of gestational diabetes mellitus. Chinese Journal of Practical Gynecology and Obstetrics, 31(01), 91-94.
[4] Willow. Type 1 diabetes? Type 2 diabetes? Dual diabetes? Shandong University, 2013.
[5] Cui Wenxiang. Health problems and educational intervention strategies for adolescents with type 1 diabetes [J] . Clinical Journal of Practical Pediatrics, 2008, 23(8) : 628-630. DOI: 10.3760/cma.j.issn.2095-428X.2008.08.128.
[6] Weng Jianping. Guangdong Medicine, 2012, 33(18): 2699-2702.DOI: 10.13820/j.cnki.gdyx.2012.18.030.
[7] Zhong Guanguan. Epidemiological research on type 2 diabetes [J]. Chinese Medical Guide, 2011, 9(13): 124-125.DOI: 10.15912/j.cnki.gocm.2011.13.143.
[8] Xiao Xinhua. New Progress in the Treatment of Type 1 Diabetes [J]. Foreign Medicine. Journal of Endocrinology, 2004, (04): 281-282.
[9] American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2021 [J]. Diabetes Care, 2021, 44(Suppl 1): S15-S33. DOI: 10.2337/dc21-S002.
[10] Luciani L, Pedrelli M, Parini P. Modification of lipoprotein metabolism and function driving atherogenesis in diabetes [J]. Atherosclerosis, 2024, 394: 117545. DOI: 10.1016/j.atherosclerosis.2024.117545.
[11] Singh A, Shadangi S, Gupta PK, et al. Type 2 diabetes mellitus: a comprehensive review of pathophysiology, comorbidities, and emerging therapies [J]. Compr Physiol, 2025, 15(1): e70003. DOI: 10.1002/cph4.70003.
[12] Thal SC, Shityakov S, Salvador E, et al. Heart rate variability, microvascular dysfunction, and inflammation: exploring the potential of taVNS in managing heart failure in type 2 diabetes mellitus [J]. Biomolecules, 2025, 15(4): 499. DOI: 10.3390/biom15040499.

[13] He Xing, Tian Hong, Xu Song, et al. Modern Medicine & Clinical, 2009, 24(3): 5.DOI: CNKI: SUN: GWZW.0.2009-03-000.
[14] Bao Yuqian, Jia Weiping. New drugs and new strategies for the treatment of diabetes [J]. China Journal of New Drugs and Clinic, 2011, 30(6): 2.DOI: CNKI: SUN: XYYL.0.2011-06-003.
[15] Zeng Jing, Fang Yi. Current status and drug research progress of diabetes mellitus drug therapy [J]. Journal of Clinical Drug Therapy, 2017, 15(10): 5.DOI: 10.3969/j.issn.1672-3384.2017.10.001.
[16] Neumann A, Weill A, Ricordeau P, et al. Pioglitazone and risk of bladder cancer among diabetic patients in France: a population-based cohort study [J]. Diabetologia, 2012, 55(7): 1953-1962.
[17] Conget I, Aronson R, Lee S, et al. Comment on Home et al. Insulin therapy in people with type 2 diabetes: opportunities and challenges? [J]. Diabetes Care, 2014, 37(11): e245.
[18] Weng Jianping. Consensus on the clinical application of glucagon-like peptide 1 hypoglycemic drugs [J]. Chinese Journal of Diabetes, 2014(1): 7.DOI: 10.3760/cma.j.issn.1674-5809.2014.01.004.
[19] Nathan DM. Diabetes: Advances in diagnosis and treatment [J]. JAMA, 2015, 314( 10): 1052-1062
[20] Cuddihy RM,Philis-Tsimikas A,Nazeri A． Type 2 diabetes care and insulin intensification: is a more multidisciplinary approach needed? Results from the MODIFY survey[J]． Diabetes Educ, 2011,37( 1): 111-123
[21] Wang Xiaoqing, Yin Lianghong, Qian Yongchang. FGF1: a novel potential drug for the treatment of diabetes [J]. Chinese Journal of Biochemistry and Molecular Biology, 2018, 34(10): 8.DOI: CNKI: SUN: SWHZ.0.2018-10-003.
[22] Suh JM,Jonker JW,Ahmadian M,et al. Endocrinization of FGF1 produces a neomorphic and potent insulin sensitizer [J]. Nature,2014,513( 7518) : 436-439
[23] Scarlett JM, Rojas JM, Matsen ME, et al. Central injection of fibroblast growth factor 1 induces sustained remission of diabetic hyperglycemia in rodents [J]. Nat Med, 2016, 22 ( 7): 800-806
[24] Wang B, Chandrasekera PC, Pippin JJ. Leptin- and leptin receptor-deficient rodent models: relevance for human type 2 diabetes [J]. Curr Diabetes Rev, 2014, 10( 2): 131-145
[25] Chandrasekera PC, Pippin J J. Of rodents and men: species specific glucose regulation and type 2 diabetes research [J]. ALTEX, 2014, 31( 2): 157-176
[26] Zhang H, Zhu X, Li X, et al. Pharmacokinetics and pharmacodynamics of rongliflozin, a novel selective inhibitor of sodium-glucose co-transporter-2, in peo ple with type 2 diabetes mellitus [J]. Diabetes Obes Metab, 2020, 22(2): 191-202.
[27] Saxena AR, Frias JP, Brown LS, et al. Efficacy and safe ty of oral small molecule glucagon-like peptide 1 re ceptor agonist danuglipron for glycemic control among patients with type 2 diabetes [J]. JAMA Net work Open, 2023, 6(5): e2314493.
[28] Saxena AR, Frias JP, Gorman DN, et al. Tolerability, safety and pharmacodynamics of oral, small- mole cule glucagon-like peptide-1 receptor agonist danug lipron for type 2 diabetes: A 12-week, randomized, placebo-controlled, Phase 2 study comparing differ ent dose- escalation schemes [J]. Diabetes Obes Metab, 2023, 25(10): 2805-2814.
[29] Du Y, Gao L, Xiao X, et al. A multicentre, randomized, double-blind, parallel, active- and placebo-controlled phase 3 clinical study of the glucokinase activator PB 201 in treatment-naive patients with type 2 diabetes mellitus: A study protocol [J]. Diabetes Obes Metab, 2022, 25(3): 649-655.
[30] Xiang Kunsan. National New Bibliography, 2013(12): 2.DOI: CNKI: SUN: QGXS.0.2013-12-015.
[31] Hannon TS, Kahn SE, Utzschneider KM, et al. Review of methods for measuring βcell function: design considerations from the Restoring Insulin Secretion (RISE) Consortium [J]. Diabetes Obes Metab, 2018, 20(1): 14-24. DOI: 10.1111/dom.13005.
[32] Yang Y, Kim JW, Park HS, et al. Pancreatic stellate cells in the islets as a novel target to preserve the pancreatic βcell mass and function [J]. J Diabetes Investig, 2020, 11(2): 268280. DOI: 10.1111/jdi.13202.
[33] Ying W, Fu W, Lee YS, et al. The role of macrophages in obesityassociated islet inflammation and βcell abnormalities [J]. Nat Rev Endocrinol, 2020, 16(2): 8190. DOI: 10.1038/s4157401902863.
[34] Weir GC, Gaglia J, BonnerWeir S. Inadequate βcell mass is essential for the pathogenesis of type 2 diabetes [J]. Lancet Diabetes Endocrinol, 2020, 8(3): 249256. DOI: 10.1016/S22138587(20)30022X.
[35] Xu ZP, Saunders GF. Transcriptional regulation of the human PAX6 gene promoter. J Biol Chem. 1997 Feb 7; 272(6): 3430-6. doi: 10.1074/jbc.272.6.3430. PMID: 9013587.
[36] Galavi H, Mollashahee-Kohkan F, Saravani R, Sargazi S, Noorzehi N, Shahraki H. HHEX gene polymorphisms and type 2 diabetes mellitus: A case-control report from Iran. J Cell Biochem. 2019 Oct; 120(10): 16445-16451. doi: 10.1002/jcb.28788. Epub 2019 Jun 25. PMID: 31237015.
[37] Cauchi S, Froguel P. TCF7L2 genetic defect and type 2 diabetes. Curr Diab Rep. 2008 Apr; 8(2): 149-55. doi: 10.1007/s11892-008-0026-x. PMID: 18445358.

[38] Asghar A, Firasat S, Afshan K, Naz S. Association of CDKAL1 gene polymorphism (rs10946398) with gestational diabetes mellitus in Pakistani population. Mol Biol Rep. 2023 Jan; 50(1): 57-64. doi: 10.1007/s11033-022-08011-x. Epub 2022 Oct 27. PMID: 36301463.
[39] Rutter GA, Chimienti F. SLC30A8 mutations in type 2 diabetes. Diabetologia. 2015 Jan; 58(1): 31-6. doi: 10.1007/s00125-014-3405-7. Epub 2014 Oct 7. PMID: 25287711.
[40] Sun Yan, Wang Wenjiao, Wu Bin. Research progress on the effects of adipose tissue at different parts on apoptosis of pancreatic islets β [J]. Chinese Journal of Diabetes, 2024, 32(12): 951-953.
[41] Li Heng, Zhang Cuilan. Effect of inhibition of autophagy on cyanidin-3-O-glucoside to protect islet β cell damage in a high-sugar and high-fat environment [J]. Hebei Medicine, 2024, 30(2): 182-188.DOI: 10.3969/j.issn.1006-6233.2024.02.02.
[42] Chen Bei, Tian Ting. Research on the mechanism of ROS-mediated pyroptosis of pancreatic islets β affected the occurrence of gestational diabetes by high glucose environment [J]. Chinese Journal of Eugenics and Genetics, 2025, 33(10): 2135-2140. DOI: 10.13404/j.cnki.cjbhh.2025.10.003.
[43] Bai Juanxia, Quan Jinxing, Guo Wenyan, et al. Research progress on vitamin D intervention ferroptosis in diabetes mellitus and its complications [J/OL]. Journal of Lanzhou University(Medical Edition), 1-6 [2026-04-07]. https://link.cnki.net/urlid/62.1194.R.20260303.1013.002.
[44] Zhai Yanhui, Liang Yonglin, An Dong, et al. Research status of the mechanism of pancreatic islet β cell damage mechanism with type 2 diabetes [J]. Chinese Journal of Clinical Pharmacology, 2024, 40(16): 2442-2446.DOI: 10.13699/j.cnki.1001-6821.2024.16.030.
[45] WANG T Y,LIU X J,XIE J Y,et al. Cask methylation involved in the injury of insulin secretion function caused by interleukin1 - beta [J]. J Cell Mol Med, 2020, 24( 24) : 14247—14256.
[46] Lin Zhili, Lei Lei, Li Changrun, et al. Kinetic model and treatment strategy of type 2 diabetes mellitus caused by islet inflammation [J]. Journal of Peking University(Natural Science Edition), 2021, 57(02): 199-208. DOI: 10.13209/j.0479-8023.2020.038.
[47] Eizirik D L Darville M I. Beta-cell apoptosis and defense mechanisms:lessons from type 1 diabetes [J]. Diabetes 200150(suppl1):S64-S69.
[48] Wu Yingzhi, Liu Xu, Gao Lihui. Research progress on the protective effect of autophagy on pancreatic islet β cells [J]. International Journal of Pharmaceutical Research, 2015, 42(04): 447-452.DOI: 10.13220/j.cnki.jipr.2015.04.004.
[49] Fu Haichao, Leng Jinhong. Research progress on the effect of autophagy on apoptosis and its mechanism in pancreatic islet β cells [J]. Journal of Intractable Diseases, 2020, 19(06):632-634+639.
[50] Mizushima N, Komatsu M. Autophagy: Renovation of cells and tissues [J]. Cell, 2011, 147( 4): 728-741. DOI: 10.1016/j.cell.2011.10.026.
[51] King BC, Kulak K, Krus U,et al. Complement component c3 is highly expressed in human pancreatic islets and prevents β cell death via ATG16L1 interaction and autophagy regulation. Cell Metab, 2019, 29:202210.
[52] Kim J, Cheon H, Jeong YT, et al. Amyloidogenic peptide oligomer accumulation in autophagydeficient β cells induces diabetes. J Clin Invest, 2014, 124:33113324.]
[53] Kaniuk NA, Kiraly M, Bates H, et al. Ubiquitinatedprotein aggregates form in pancreatic betacells during diabetesinduced oxidative stress and are regulated by autophagy. Diabetes, 2007, 56:930939.
[54] Aoyagi K, Ohara IM, Itakura M, et al. VAMP7 regulates autophagy to maintain mitochondrial homeostasis and to control insulin secretion in pancreatic βCells. Diabetes, 2016, 65:16481659.
[55] Bugliani M, Mossuto S, Grano F, et al. Modulation of autophagy influences the function and survival of human pancreatic beta cells underendoplasmicreticulumstressconditionsandintype 2diabetes. Front Endocrinol(Lausanne), 2019, 10:52.
[56] Hardie DG. AMP-activated protein kinase: An energy sensor that regulates all aspects of cell function. Genes Dev, 2011, 25(18): 1895-1908.
[57] Hardie DG. AMP-activated protein kinase: A cellular energy sensor with a key role in metabolic disorders and in cancer. Biochem Soc Trans, 2011, 39(1): 1-13.
[58] Perluigi M, Di Domenico F, Butterfield DA. mTOR signaling in aging and neurodegeneration: At the crossroad between metabolism dysfunction and impairment of autophagy [J]. Neurobiology of disease, 2015, 84: 39-49.
[59] Kim J, Kundu M, Viollet B, Guan KL. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1 [J]. Nature cell biology, 2011, 13(2): 132-141.
[60] Rivera JF, Costes S, Gurlo T, et al. Autophagy defends pancreatic β cells from human islet amyloid polypeptide-induced toxicity [J].The Journal of Clinical Investigation, 2014, 124(8): 3489-3500.
[61] Wang Yujia. Research on the regulation of pancreatic islet β autophagy by the JNK/Beclin-1 pathway [D].China Medical University, 2020.

DOI: 10.54254/2753-8818/2026.33552

[62] ScherzShouval R, Elazar Z.ROS, mitochondria and the regulation of autophagy [J]. Trends in Cell Biology, 2007, 17(9): 422-427.
[63] Hartley, T., Brumell, J., & Volchuk, A. (2009). Emerging roles for the ubiquitin-proteasome system and autophagy in pancreatic beta-cells. American journal of physiology. Endocrinology and metabolism, 296(1), E1–E10. https: //doi.org/10.1152/ajpendo.90538.2008
[64] Marsh BJ, Soden C, Alarcón C, et al. Regulated autophagy controls hormone content in secretory-deficient pancreatic endocrine beta-cells [J]. Molecular En docrinology, 2007, 21(9): 2255-2269.
[65] Chakraborty S, Rasool RU, Kumar S, et al. Cristacarpin promotes ERS -mediated ROS generation leading to premature senescence by activation of p21waf-1. Age(Dordr), 2016, 38:62.
[66] Chen YY, Sun LQ, Wang BA, et al. Palmitate induces autophagy in pancreatic β - cells via endoplasmic reticulum stress and its downstream JNK pathway. Int J Mol Med,2013,32:1401-1406.
[67] Ren Haiwen, Wang Linhua, Gong Quan, et al. Chinese Journal β of Diabetes, 2022, 30(10): 796-800.DOI: 10.3969/j.issn.1006.
[68] Marasco MR, Conteh AM, Reissaus CA, et al. Interleukin - 6 reduces β - cell oxidative stress by linking autophagy with the antioxidant response. Diabetes, 2018, 67:1576-1588.
[69] Linnemann AK, Blumer J, Marasco MR, et al. Interleukin 6 protects pancreatic β cells from apoptosis by stimulation of autophagy. Faseb J, 2017, 31:4140-4152.
[70] Ozcan U, Cao Q, Yilmaz E, et al. Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes [J]. Science, 2004, 306(5695):457-461.
[71] Halban PA. Release of incompletely processed proin sulin is the cause of the disproportionate proinsulinemia of NID DM [J]. Diabetes, 1997, 46(11):1725-1732.
[72] Wauson EM, Zaganjor E, Lee AY, et al. The G protein-coupled taste receptor T1R1/T1R3 regulates mTORC1 and autophagy [J]. Mol Cell, 2012, 47(6):851-862.