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β-cell neogenesis: A rising star to rescue diabetes mellitus

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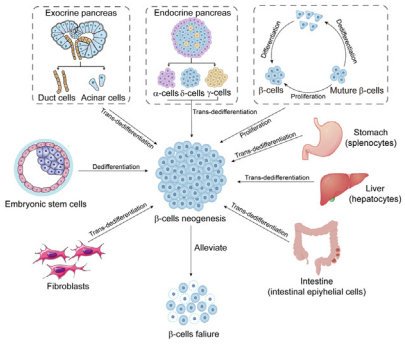
HIGHLIGHTS

- Progressive β-cell failure is central to the pathophysiological mechanisms of insulin-deficient diabetes mellitus.
- The molecular mechanisms of β-cell failure engage multiple biological processes such as genetic susceptibility, endoplasmic reticulum (ER) stress, oxidative stress, islet inflammation, and protein modifications linked to multiple signaling pathways.
- The potential source of β-cell neogenesis include stimulating existing β-cell proliferation, promoting stem cell differentiation, and directing *trans*-differentiation of non-β-cells in the endocrine pancreas (α-cells, δ-cells, and γ-cells) and exocrine pancreas (acinar cells and ductal cells), as well as other tissues and cells such as the liver, pancreas, intestine, and endocrine progenitor-like cells.

GRAPHICAL ABSTRACT



Abbreviations: T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus; GWAS, Genome-wide association studies; ER, Endoplasmic reticulum; PERK, Pancreatic ER kinase (PKR)-like ER kinase; IRE1, Inositol-requiring enzyme 1; ATF6, Activating transcription factor 6; eIF2aZ, Eukaryotic translation initiation factor-2a; ATF4, Activating transcription factor 4; CHOP, C/EBP-homologous protein; TRAF2, TNF receptor-associated factor 2; ATF3, Activating transcription factor 3; XBP1, X-box binding protein 1; FFA, Free fatty acid; JNK, c-Jun N-terminal kinase; HBP, Hexosamine biosynthesis pathway; ERK, Extracellular signal-regulated kinase; GSIS, Glucose-stimulated insulin secretion; PDX1, Pancreatic and duodenal homeobox 1; BETA2, β-cells E-box transcriptional activator 2; MAFA, V-maf musculoaponeurotic fibrosarcoma oncogene homologue A; C/EBP-β, CCAAT/enhancer binding protein β; ROS, Reactive oxygen species; RNS, Reactive nitrogen species; NF-κB, Nuclear factor κB; p38 MAPK, P38 mitogen-activated proteinkinases; AMPK, Amp-activated protein kinase; Bax, BCL2-Associated X; AKT, Protein Kinase B; FOXO1, Forkhead box protein O1; NGN3, Nsulin-secreting-neurogenin3; NLRP3, nucleotide binding oligomerisation domain (NOD)-, leucine-rich repeat (LRR)- and pyrin domain-containing protein 3; IL-6, Interleukin-6; IL-1β, Interleukin-1β; SOX9, SRY-related high-mobility-group-box gene 9; HES1, Hairy and enhancer of split; PKC-δ, Protein kinase C-δ; IFN-γ, Interferon γ; O-GlcNAcylation, O-linked N-acetylglucosamine glycosylation; UDP-GlcNAc, Uridine diphosphate N-acetylglucosamine; OGT, O-GlcNAc transferase; OGA, O-GlcNAcase; Mef2d, Myocyte enhancer factor 2D; Nrf2, Nuclear factor erythroid-2-related factor 2; CDK, Cyclin-dependent protein kinase; mTORC1, mammalian target of rapamycin complex 1; ESCs, embryonic stem cells; ASCs, Adult stem cells; PI3K, Phosphatidylinositol 3-kinase; FGF4, Fibroblast growth factor 4; NADP, Nicotinamide adenine dinucleotide phosphate; GABA, γ-Aminobutyric acid; GSK-3, glycogen synthase kinase-3; GLP-1, Glucagon-like peptide-1; GLP-1 RAs, GLP-1 receptor agonists; DPP-IV, Enzyme dipeptidyl peptidase IV; STZ, Streptozotocin.

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ABSTRACT

Background: Diabetes Mellitus (DM), a chronic metabolic disease characterized by elevated blood glucose, is caused by various degrees of insulin resistance and dysfunctional insulin secretion, resulting in hyperglycemia. The loss and failure of functional β-cells are key mechanisms resulting in type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM).
Aim of review: Elucidating the underlying mechanisms of β-cell failure, and exploring approaches for β-cell neogenesis to reverse β-cell dysfunction may provide novel strategies for DM therapy.
Key scientific concepts of review: Emerging studies reveal that genetic susceptibility, endoplasmic reticulum (ER) stress, oxidative stress, islet inflammation, and protein modification linked to multiple signaling pathways contribute to DM pathogenesis. Over the past few years, replenishing functional β-cell by β-cell neogenesis to restore the number and function of pancreatic β-cells has remarkably exhibited a promising therapeutic approach for DM therapy. In this review, we provide a comprehensive overview of the underlying mechanisms of β-cell failure in DM, highlight the effective approaches for β-cell neogenesis, as well as discuss the current clinical and preclinical agents research advances of β-cell neogenesis. Insights into the challenges of translating β-cell neogenesis into clinical application for DM treatment are also offered.

Contents

Introduction

Diabetes mellitus (DM), is a severe chronic endocrine system disorder characterized by a hyperglycemic condition, leading to multiple complications, including diabetic foot, diabetic nephropathy, diabetic retinopathy, and cardiovascular disease [1]. Based on its etiology, DM is primarily classified into type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). The insulin-producing β-cells are lost in T1DM as a result of autoimmune-mediated disruption, resulting in a complete insulin deficiency. In T2DM, the defective β-cell function and the resistance to insulin cause relative insulin deficiency [2]. Thus, the essence of the pathogenesis of DM is an absolute or relative inadequacy in insulin secretion. At the onset of DM, there is a notable β-cell failure, making it inadequate to sustain normal glucose metabolism [3].

Currently, exogenous insulin injections and oral hypoglycemic drugs can only relieve the symptoms of hyperglycemia and alleviate the occurrence of DM complications but often fail to prevent the progressive decline of β-cells function. Pancreas or islet transplantation offers a prospective treatment for DM, however, immune rejection, surgical challenges, donor-recipient (D-R) matching issues, and donor shortage limit its clinical application [4,5]. Therefore, elucidating the fundamental mechanisms of β-cell failure, and exploring the approaches for β-cell neogenesis to reverse β-cell dysfunction, may provide novel strategies for DM therapy.

Previously, several researchers separately reviewed β-cell neogenesis with a specific focus on the strategies of β-cell regeneration [6–11], whereas lacking the elucidation of the mechanisms of β-cell failure and delineation of the comprehensive routes of targeting β-cell neogenesis. Importantly, given the remarkable advances and emergence of novel findings in this field, we are encouraged to make a contribution to elaborating the understanding of the mechanisms of progressive β-cell failure with comprehensive and different viewpoints based on a vast array of recent experimental and clinical studies and propose a number of novel and promising strategies to restore β-cell mass and function through β-cell neogenesis. Particularly, the preclinical and clinical drugs targeting β-cell neogenesis for DM therapy, including synthetic drugs and phytochemical compounds, are also reviewed. Moreover, we discuss the current challenges and limitations of targeting β-cell neogenesis for DM treatment. We hope that such a review article could provide some newfound knowledge and references for the early translation to clinical applications of β-cell neoplasia against DM in the background of a heavy global health burden on DM.

β-cell failure in DM

When the number of functional β-cells decreases below physiological levels, progressive functional β-cell failure develops, making it impossible for the body to sustain a normal metabolism of glucose. The categories ascribed to functional islet β-cell failure are as follows [12]: (1) decreased β-cell number: histologically confirmed β-cell number decline involves increased β-cell apoptosis [13,14], (2) β-cells dysfunction: a chronic load on β-cells results in normal β-cells failing to produce insulin against glucose [15,16], and (3) β-cell identity loss (dedifferentiation and *trans*-differentiation of β-cells): dedifferentiation of islet β-cells is defined as the regression of mature β-cells into less differentiated or precursor-like forms followed by the loss of differentiated phenotypes and cellular properties as exposure to appropriate conditions such as high levels of glucose, lipids, and inflammatory cytokines [17]. β-cells dedifferentiation is reversible. The dedifferentiated or reprogrammed β-cells can recover to their originally intended identities under appropriate conditions, including inhibition of the TGF-β pathway, insulin therapy, and blood glucose normalization [18–20]. β-cells can also transdifferentiate into other endocrine cells, e.g., the characteristically expressed genes of α- and δ-cells become activated among β-cells enabling β-cells *trans*-differentiation into α- and δ-cells, respectively [21,22].

β-cell failure performs a pivotal function in T1DM and T2DM pathogenesis, where T1DM arises from β-cell failure mediated by autoimmune destruction, requiring life-long exogenous insulin therapy [23]. T2DM is mainly triggered by the progressive loss of β-cells that produce insulin. During the early stages of T2DM, the functional β-cells mass, both in terms of their quality and number, appears to reduce in the course of insulin secretion [24]. Hence, gaining insight into the mechanism behind β-cell failure is crucial for preventing or treating T1DM and T2DM.

Mechanisms of β-cell failure

Pancreatic β-cell failure refers to a combination of reduced β-cell numbers, β-cell dysfunction and β-cell identity loss, which are strongly correlated with DM occurrence [12]. β-cells losing identity tend to dedifferentiate into nonfunctional endocrine progenitor-like cells or *trans*-differentiate into pancreatic non-β-cells types [25]. To date, the cause explaining the loss of β-cell identity is still poorly understood. A comprehensive understanding of β-cell failure would be helpful in devising effective countermeasures to restore β-cell number and function. Here, we elaborate on the underpinning mechanisms of β-cell failure and its related signaling pathways.

Genetics factors

Genetic factors are intimately related to the pathogenesis of DM, as illustrated by the higher concordance rate of this disorder in monozygotic twins [26,27]. In the last decades, genome-wide association studies (GWAS) have identified more than 50 genomic locations related to T1DM [28] and over 400 genes affecting T2DM [29]. These genomic regions or genes impact β-cell mass or function [30]. For instance, the variants in the WFS1 gene lead to β-cell dysfunction and increase the risk of DM [31,32]. In mice models, knockout of NeuroD1, Pax4, or Pax6 results in a decrease in β-cell number or absence of β-cells at birth [33–35]. Also, heterozygous PDX1 ($PDX1^{+/-}$) mice with 50 % depletion in PDX1 were characterized by a reduction in β-cells mass and the progressive development of glucose intolerance, suggesting that PDX1 modulates β-cells mass and function [36].

Additionally, the influences of genetic factors on β-cell failure are also mirrored in ethnic differences in human and animal models. For example, β-cell failure in a cohort of European ancestry does not necessarily lead to total β-cell depletion in T1DM [37,38]. Instead, during long-term follow-up, complete insulin secretion loss was often observed among the Japanese population [39]. In patients with T2DM, it has also been observed that, unlike populations of European descent, Japanese have a low insulin secretory capacity, tending to develop T2DM with no or mild obesity [40,41]. In different strains of mice with equal levels of pathological obesity, C57BL/6J were resistant to obesity–induced DM and suffered from mild and transient DM only, while C57BL/KsJ mice underwent serious DM along with progressive β-cell failure and apoptosis [42,43]. The genetically dependent β-cell resistance against obesity-related metabolic stress may determine these differences. In mice models, mutations in leptin and its receptor are well recognized to develop obesity and DM with β-cell failure [44]. Undoubtedly, no single genetic variant governs β-cell failure, ultimately contributing to DM. More comprehensive and in-depth genetic studies will be necessary to further comprehend the genetic factors behind β-cell failure among DM patients.

Endoplasmic reticulum (ER) stress

ER stress refers to various physiological or pathological factors, such as hypoxia, hyperglycemia, inflammatory states, etc., which lead to the accumulation of misfolded and unfolded proteins in the ER lumina and disturbed calcium ion homeostasis [45]. Notably, the chronic glucose toxicity, lipotoxicity, and inflammatory states in the DM environment disrupt ER homeostasis, causing a

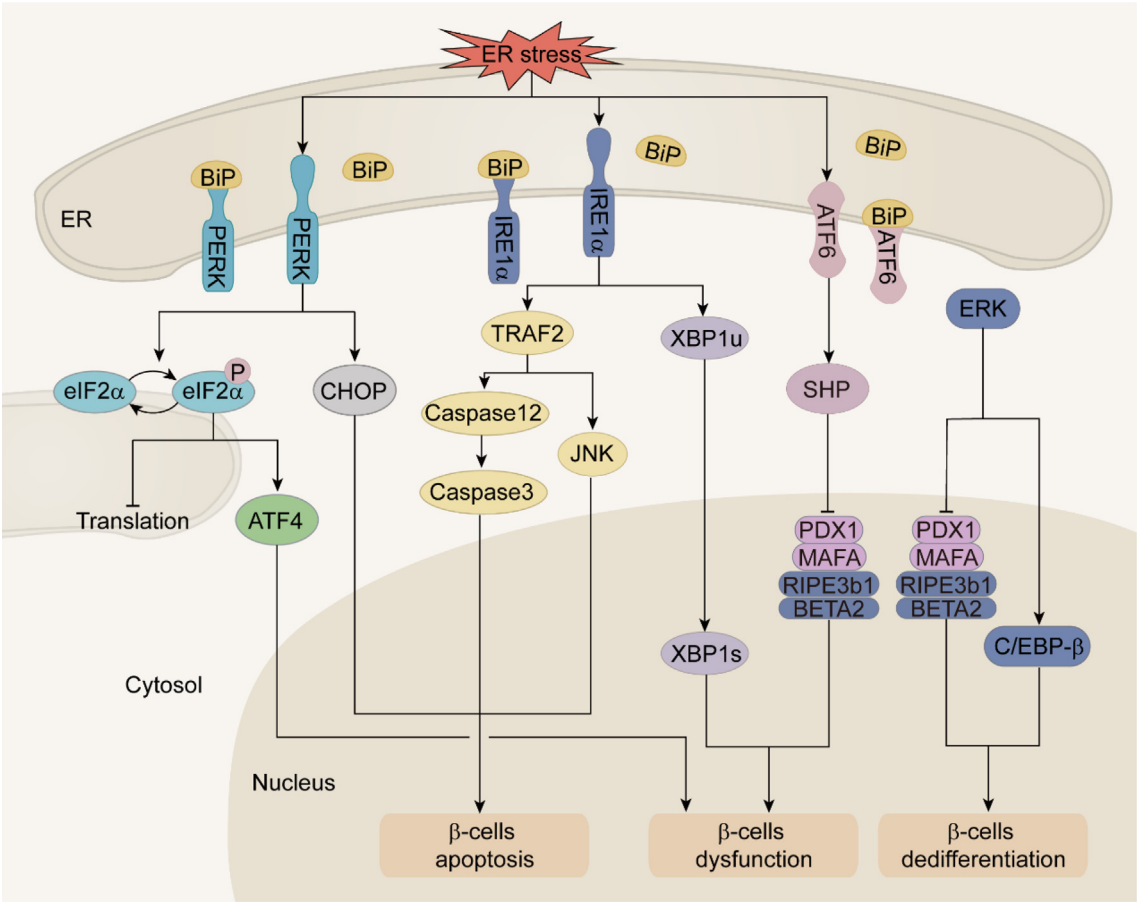

Fig. 1. ER stress promotes β-cell failure through multiple pathways. The ER membrane-localized stress transducers PERK, IRE1, and ATF6 are activated upon dissociation from BiP in response to sustained ER stress. Firstly, activated PERK decreases overall mRNA translation by phosphorylating eIF2α and causes impaired insulin secretion and apoptosis by facilitating the expression of ATF4 and CHOP, respectively. Secondly, activated IRE1 cuts off XBP1, leading to insulin mRNA degradation and reduced insulin synthesis, and also triggers β-cell apoptosis through TRAF2 activating caspase-12 and JNK pathways. Thirdly, activated ATF6 represses the expression of the β-cell-rich transcription factors PDX1, BETA2, and RIPE3b1/MafA via upregulation of SHP expression, ultimately leading to β-cell dysfunction. Finally, ER stress triggers β-cell dedifferentiation by activating ERK pathways. ER, Endoplasmic reticulum; PERK, Pancreatic ER kinase (PKR)-like ER kinase; IRE1, Inositol-requiring enzyme 1; ATF6, Activating transcription factor 6; eIF2aZ, Phosphorylating eukaryotic translation initiation factor-2a; CHOP, C/EBP-homologous protein; XBP1, X-box binding protein 1; TRAF2, TNF receptor associated factor 2; JNK, c-Jun N-terminal kinase; SHP, Small heterodimer partner; ERK, Extracellular regulated protein kinases; PDX1, Ancreatic and duodenal homeobox 1; BETA2, β-cell E-box transcriptional activator 2; MAFA, v-maf musculoaponeurotic fibrosarcoma oncogene homologue A; C/EBP-β, CCAAT/enhancer binding protein β.

prolonged ER stress response that accelerates β-cells failure [46 47] (Fig. 1). ER stress also gives rise to ER calcium leakage by interfering with the function of the calcium channel ryanodine receptor on the ER membrane of β-cells, which in turn causes impassible insulin secretion and ultimately induces β-cells mortality [48].

Typically, the ER stress response signals are modulated by three primary ER transmembrane receptor proteins (Fig. 1): pancreatic ER kinase (PKR)-like ER kinase (PERK), inositol-requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6). Under normal physiological circumstances, three of these ER stress receptors lose activity via binding to the ER molecular chaperone binding immunoglobulin protein (BiP). With the persistent ER stress response, BiP is separated from these receptors, which drives the conversion of ER stress signals from facilitating survival to promoting apoptosis: (a) PERK activation phosphorylates eukaryotic translation initiation factor-2a (eIF2aZ), reduces the overall translation of mRNA, but activates several transcription factors, e.g., transcription factor 4 (ATF4) [49]. Overexpression of ATF4 that impairs the function of postnatal β-cells was reported [50] (Fig. 1). During coping with ER stress, PERK also exerts a pro-apoptotic effect in β-cells via upregulation of the key downstream effector's C/EBP-homologous protein (CHOP) (Fig. 1) [51]; (b) Activation of IRE1 cuts off X-box binding protein 1 (XBP1), causing insulin mRNA degradation and a decrease in insulin synthesis, and also triggers pro-apoptotic signaling in β-cells by activating caspase-12 and JNK signals via TNF receptor-associated factor 2 (TRAF2) (Fig. 1) [52]; (c) The ER stress–induced ATF6 activation suppresses the β-cell-enriched transcription factors pancreatic duodenal homeobox factor-1(PDX1), β-cells E-box transcriptional activator 2 (BETA2), and RIPE3b1/v-maf musculoaponeurotic fibrosarcoma oncogene homologue A (MAFA) expression via upregulation of small heterodimer partner (SHP) gene expression, thus leading ultimately to β-cell dysfunction and glucose-stimulated insulin secretion (GSIS) functional impairment (Fig. 1) [53]. In comparison with the non-DM counterpart, ATF6 was markedly elevated in the islets of diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats [53].

Notably, persistent activation of transcription factor 3 (ATF3) was also detected in the human islets of T1DM and T2DM cadaveric donors [54]. Clinically, the expression levels of ER stress-positive regulators, e.g., BiP, XBP1, and CHOP, were significantly elevated in pancreatic sections of T1DM human donors compared to healthy subjects, indicating that ER stress facilitates the onset of T1DM [55]. Similarly, in patients with T2DM with β-cell failure,

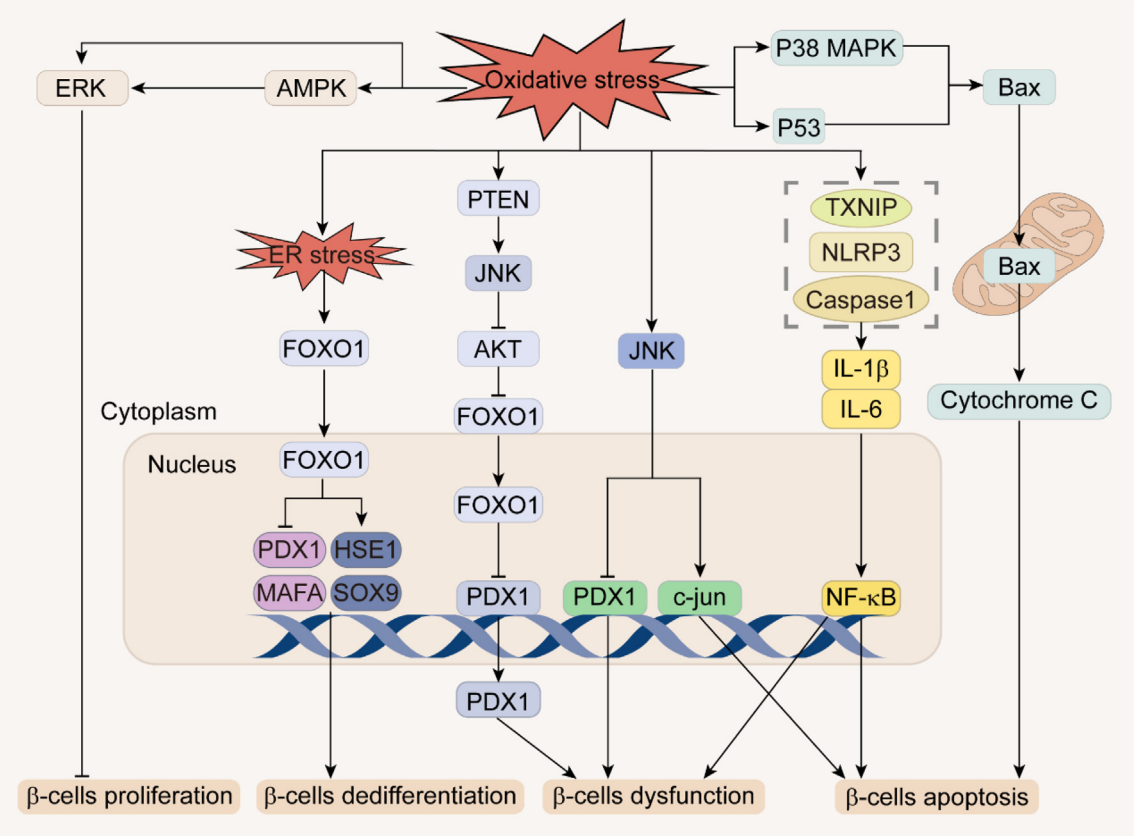

Fig. 2. The signaling pathways of oxidative stress-inducing β-cells failure. Chronic hyperglycemia disturbs the balance between ROS production and antioxidant defense function *in vivo*, resulting in oxidative stress. During this process, oxidative stress could activate the ERK or AMPK-ERK pathway, inhibiting the β-cells proliferation. Moreover, oxidative stress also suppresses insulin gene expression via the PTEN-JNK-AKT-FOXO1-PDX1 axis, or JNK activation directly decreases PDX1 binding activity to DNA, thus triggering β-cell dysfunction. Additionally, oxidative stress triggers β-cell apoptosis via the JNK/c-jun, inducible inflammasome NLRP3-activated NF-κB, p38MAPK, and p53 pathways. Finally, oxidative stress could also lead to β-cell dedifferentiation by inducing ER stress-mediated shuttling of FOXO1 to the nucleus. ROS, Reactive oxygen species; ERK, Extracellular regulated protein kinases; AMPK, Amp-activated protein kinase; PTEN, Phosphatase and Tensin Homolog deleted on Chromosome 10; JNK, c-Jun N-terminal kinase; AKT, Protein Kinase B; FOXO1, Forkhead box protein O1; PDX1, Pancreatic duodenal homeobox factor-1; NLRP3, nucleotide-binding oligomerisation domain (NOD)-, leucine-rich repeat (LRR)- and pyrin domain-containing protein 3; NF-κB, Nuclear factor κB; p38MAPK, P38 mitogen-activated protein kinases; Bax, BCL2-Associated X; ER, Endoplasmic reticulum.

increased protein expression levels of p58IPK, ATF3, CHOP, and BiP were also observed in β-cells [56,57].

Moreover, the ER stress induced by chronic hyperglycemia also triggers β-cell dedifferentiation. In INS-1E cells and murine islets, glucotoxic ER stress elicits β-cell dedifferentiation and impaired GSIS via the extracellular signal-regulated kinase (ERK)1/2 (Fig. 1) [58]. The activation of the ERK1/2 pathway caused this phenomenon, likely by affecting transcriptional or post-translational pathways to decrease the PDX1, BETA2, and MAFA expression, enhances CCAAT/enhancer binding protein β (C/EBP-β) expression [58]. Undoubtedly, maintaining ER homeostasis is essential for protecting pancreatic β-cells from β-cell failure.

Oxidative stress

Oxidative stress refers to the excessive production and/or reduced clearance of reactive molecules such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), which disturbs the balance between ROS production and antioxidant defense function in the body [59]. Accumulating research reveals the crucial role of oxidative stress in regulating hyperglycemia–induced β-cell failure (Fig. 2). Chronic hyperglycemia in β-cells disturbs normal physiological glucose metabolism via oxidative phosphorylation, which contributes to mitochondrial malfunction and ROS production, leading to β-cells failure [60]. Pancreatic islets with reduced expression levels of intrinsic antioxidant defense enzymes (catalase and glutathione peroxidase) [61] are less capable of repairing oxidatively damaged DNA, which prompts pancreatic β-cells to be especially susceptible to sustained elevations in ROS caused by high glucose concentrations [62]. It is reported that islets isolated from DM patients, when treated with reactive oxygen scavengers, which could ameliorate the insulin secretion function of β-cells [63].

Mechanistically, ROS could drive β-cell failure through various pathways, including ERK, c-Jun N-terminal kinase (JNK), p38 mitogen-activated protein kinases (p38 MAPK), p53, AMP-activated protein kinase (AMPK), nuclear factor κB (NF-κB), protein kinase B (AKT), nucleotide-binding oligomerization domain (NOD), leucine-rich repeat (LRR) and pyrin domain-containing protein 3 (NLRP3) pathways (Fig. 2) [64,65]. The study by Zhang et al. (2013) demonstrated that ROS inhibited the proliferation of rat β-cells by directly activating the ERK or AMPK-ERK signaling pathway (Fig. 2) [66]. The increased ROS also triggered β-cell apoptosis via activating p38MAPK, p53, and NF-κB pathways, accompanied by translocation of BCL2-associated X (Bax) into the mitochondria and enhanced cytochrome *C* expression and its release from the mitochondria into the cytoplasm (Fig. 2) [67]. In NIT-1 β-cells exposed to palmitate and oleate (free fatty acids, FFAs), elevated ROS induces phosphatase and tensin homolog deleted on chromosome 10 (PTEN)-dependent JNK activation and protein kinase B

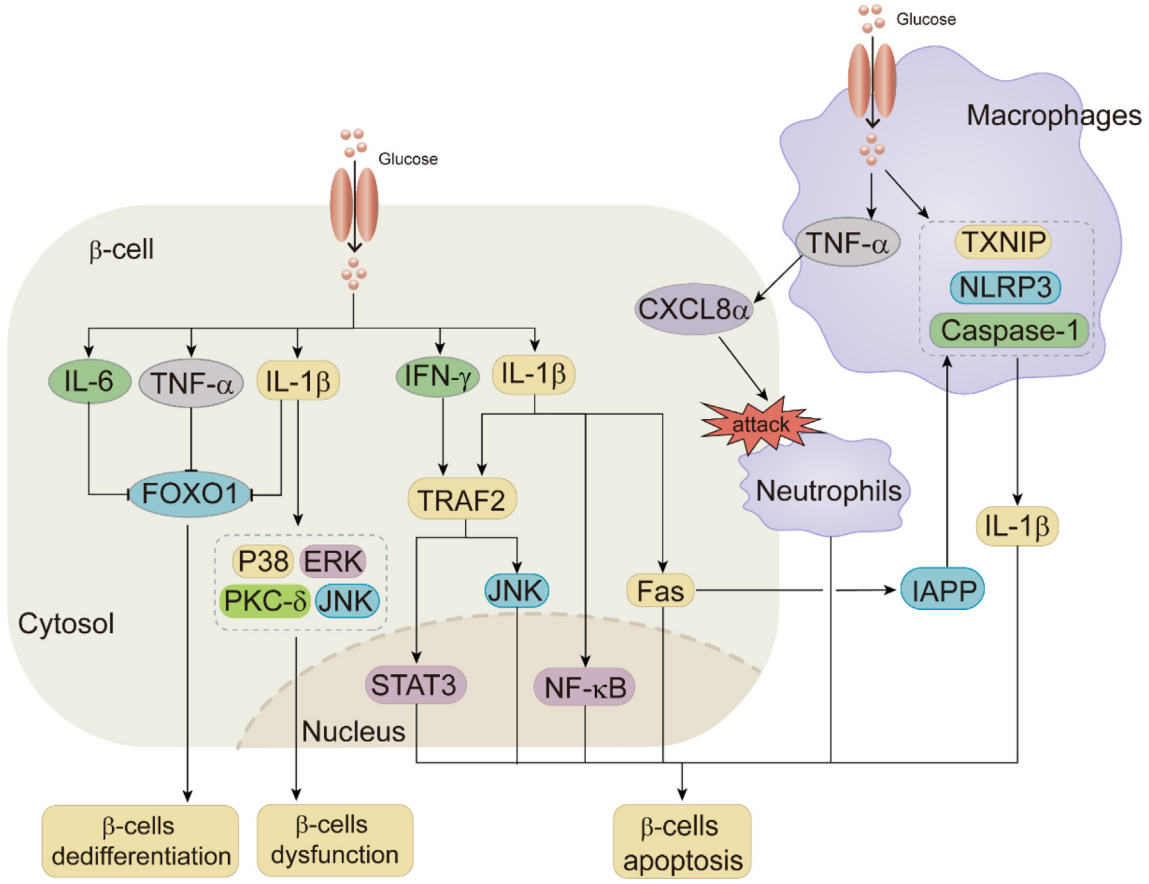

Fig. 3. The role of islet inflammation in β-cell failure. Macrophage infiltration and inflammatory factor release are increased in the chronic DM islet inflammatory milieu. β-cells produce cytokines such as IL-1β, TNF-α, and IL-6 in response to high glucose levels. The cytokine IL-1β could lead to Fas receptor upregulation and NF-κB, ERK, p38, JNK, and PKC-δ pathway activation to suppress β-cell secretion of insulin and promote apoptosis. Moreover, IL-1β and IFN-γ drive apoptosis of β-cells through TRAF2 activation of JNK and STAT3, respectively. The macrophage-derived TNF-α upregulates Cxcl8a expression in β-cells, which subsequently recruits neutrophils to attack macrophage-contacted β-cells and causes their apoptosis. Besides, the cytokines IL-1β, IL-6, and TNF-α reduce the expression of FOXO1, which maintains β-cell identity, thereby promoting β-cell dedifferentiation. Lastly, the high concentration of aggregated IAPP in islet β-cells of T2D patients not only caused β-cell apoptosis but also promoted IL-1β secretion in the microenvironment by recruiting and activating NLRP3-dependent inflammasomes in macrophages, which exacerbated the chronic inflammatory response of islets and further impaired β-cell function. IL-1β, Interleukin-1β; TNF-α, Tumor necrosis factor-α; IL-6, Interleukin-6; Fas, TNF receptor superfamily, member 6; NF-κB, Nuclear factor kB; ERK, Extracellular regulated protein kinases; P38 mitogen-activated protein kinases; JNK, c-Jun N-terminal kinase; PKC-δ, Protein kinase C-δ; IFN-γ, Interferon γ; TRAF2, TNF receptor associated factor 2; STAT3, Signal transducer and activator of transcription 3; NLRP3, nucleotide binding oligomerisation domain (NOD)-, leucine-rich repeat (LRR)- and pyrin domain-.

(AKT) inhibition, leading to the translocation of forkhead box protein O1 (FOXO1) from cytoplasm to nucleus and PDX-1 from nucleus to cytoplasm. Ultimately, this results in reduced insulin secretion with β-cell dysfunction (Fig. 2) [67]. Hydroxysafflower Yellow A (HSYA), a natural bioactive compound derived from safflower (*Carthamus tinctorius L.*) [68], has been reported to reduce apoptosis and inhibit high glucose–induced oxidative stress in INS-1 rat insulinoma cells via the JNK/c-jun pathway to improve β-cell function (Fig. 2) [69]. Additionally, the activation of JNK induced by ROS in β-cells could directly reduce the binding activity of PDX1 to DNA, contributing to decreased insulin gene expression (Fig. 2) [70].

Oxidative stress is acknowledged as an activator of NLRP3 [71], therefore NLRP3 is doomed to be engaged in oxidative stress–induced β-cell failure. In the mouse model, NLRP3-deficient islets exhibited preserved function and were protected from oxidative stress–induced cell death when compared to wild-type group islets, indicating that disruption of the NLRP3 could alleviate oxidative stress–induced β-cell apoptosis to enhance insulin production (Fig. 2) [65].

Furthermore, oxidative stress also elicited FOXO1 shuttling to the nucleus via inducing ER stress, which leads to decreased expression of β-cell maturation genes MAFA and PDX1, increased endocrine progenitor marker SRY-related high mobility group box gene 9 (SOX9), and hair and enhancer division (HES1), eventually causing β-cell dedifferentiation (Fig. 2) [72].

Islet inflammation

The inflammatory features of diabetic islets include macrophage infiltration and enhanced inflammatory factor production [73,74]. Generally, excessive nutrition causes fat, muscle, liver, and other tissues to produce a large number of inflammatory substances, which travel along with the blood flow to the islets, causing an islet inflammatory response [75]. Additionally, high metabolites such as hyperglycemia and hyperlipidemia also directly affect the islets, triggering an inflammatory response. Under the high glucose and high lipid conditions, β-cells secrete a variety of inflammatory factors, e.g. tumor necrosis factor-α (TNF-α), IL-1 β, and IL-6 (Fig. 3) [76,77].

High glucose triggers the generation and secretion of IL-1β in human islet β-cells, resulting in the upregulation of the Fas receptor (Apo-1/CD95), activation of NF-κB, apoptosis, and dysfunction of β-cells (Fig. 3) [78]. Fas, a type 1 transmembrane protein, is a

member of the tumor necrosis factor receptor (TNFR) family and triggers apoptosis by binding to the Fas ligand (FasL) [79]. Moreover, IL-1β induces β-cell apoptosis via a variety of mechanisms such as MAP/SAPKs ERK, p38, JNK, protein kinase C-δ (PKC-δ), and Ca^{2+} influx, which cause impaired insulin secretion (Fig. 3) [80–82]. The cellular toxic action of IL-1β on β-cells is also synergistically enhanced by interferon-γ (IFN-γ) and TNF-α [83]. IL-1β and IFN-γ drive apoptotic death of β-cells through activation of the TNF receptor associated factor 2 (TRAF2)-mediated JNK and signal transducer and activator of transcription 3 (STAT3) pathways (Fig. 3) [84]. It's important to note that prolonged exposure to inflammatory factors like IL-1β, IFN-γ, and TNF-α, suppresses Ca^{2+}-ATPase (sarco endoplasmic reticulum Ca^{2+}-ATPase, SERCA) to deplete the ER calcium reservoir, leading to impaired insulin secretion [85]. Interestingly, recent studies found that inflammation–induced β-cell loss also requires islet immune cells engagement. Under the condition of islet inflammation, macrophage-derived TNF-α promotes upregulation of chemokine (C-X-C motif) ligand 8a (Cxcl8a) in β-cells, which is a potent activator and chemoattractant of neutrophils, thereby enlisting neutrophils to attack β-cells in contact with macrophages to cause their apoptosis (Fig. 3) [86].

Besides, inflammation is also implicated in β-cell dedifferentiation. A clinical study demonstrates that the proportion of dedifferentiated β-cells is significantly enhanced among non-DM chronic pancreatitis and T2DM sufferers, indicating that pancreatic inflammation might promote islet β-cell loss of differentiation and ultimately lead to β-cell failure [87]. In cultivated human and mouse islets, the inflammatory factors IL-6, IL-1β, and TNF-α also diminished the transcription factor FOXO1 expression that maintains β-cell properties, contributing to β-cell dedifferentiation. (Fig. 3) [88]. Clinically, a decreased pancreatic β-cell mass in T2DM sufferers is accompanied by islet amyloid polypeptide (IAPP) deposition that is correlated with the inflammatory response [89]. High concentrations of aggregated IAPP not only cause β-cell apoptosis but also facilitate IL-1β processing and secretion in the microenvironment by recruiting and activating NLRP3-dependent inflammasomes in macrophages, which exacerbated the chronic inflammatory response of islets and further impaired β-cell function (Fig. 3) [90,91].

Protein post-translational modification (PTM)

O-linked n-acetylglucosaminylation (O-GlcNAcylation)

Increasing evidence indicates that O-GlcNAcylation as a reversible protein post-translational modification strongly correlates with DM occurrence [92]. The hexosamine biosynthesis pathway (HBP) is a glycolytic shunt that generates uridine diphosphate N-acetylglucosamine (UDP-GlcNAc), a metabolic substrate of O-GlcNAcylation. O-GlcNAcylation is catalyzed by O-GlcNAc transferase (OGT) and O-GlcNAcase (OGA) for the addition and removal of O-GlcNAc, respectively. In physiological conditions, around 2–3 % of the glucose in β-cells is funneled into HBP. Under prolonged hyperglycemia, the flow of glucose into the HBP pathway is greatly enhanced, thus increasing the protein' O-GlcNAcylation [92,93]. Pancreatic β-cells are known to contain high levels of O-GlcNAc and OGT [93], and O-GlcNAcylation is essential for maintaining β-cell function [94]. Pancreatic β-cells-specific OGT-knockout mice displayed hyperglycemia, insulin depletion, and β-cell apoptosis [94]. Mechanistically, OGT has been reported to target numerous regulators of β-cells function, including PDX1, FOXO1, NeuroD1, AKT, and insulin receptor substrate 2 (IRS2) [95–97]. Enhanced O-GlcNac was revealed to facilitate β-cell glycotoxicity by regulating the expression levels of cell death-related genes [98]. Whereas, certain proteins' O-GlcNAcylation may be detrimental, leading to β-cell failure. In highly glucose-treated MIN6-K8 cells, a comprehensive immunoprecipitation proteomic analysis identified six candidate proteins for O-GlcNAcylation, among which myocyte enhancer factor 2D (Mef2d) was confirmed to negatively regulate β-cell insulin secretion via O-GlcNAcylation of Mef2d [99].

Sumoylation

SUMOylation, an evolutionarily well-conserved PTM that modulates protein subcellular localization, stability, and gene expression [100], refers to the covalent attachment of a small ubiquitin-like modifier (SUMO) protein to the lysine residues of target proteins [101]. Emerging evidence demonstrates that SUMOylation acts as a critical agent in insulin release and glucose metabolism by mediating pancreatic apoptosis and β-cell function [100]. For instance, the enhanced SUMOylation mediated by SUMO1 upregulation or sentrin-specific protease 1 (SENP1) knockdown was reported to arrest stimulus–induced cell death in INS-1 and human islet cells, which was correlated with iNOS expression reduction, caspase 3 cleavage, and NF-κB nuclear translocation [102]. The mice with a specific knockout of the SUMO-binding enzyme UBC9 experienced impaired β-cell function and quality, as well as progressive β-cell apoptosis, ultimately leading to severe DM [103].

Crosstalk among oxidative/ER stress, islet inflammation, and PTM in the modulation of β-cell failure

In hyperglycemia–induced oxidative stress, high concentrations of ROS trigger inflammasome development consisting of NLRP3, thioredoxin-interacting protein (TXNIP), and caspase-1, promoting IL-1β generation and secretion, which further exacerbates the action of inflammatory factors in β-cell failure [104]. Conversely, mimicking a chronic systemic inflammatory response by lipopolysaccharide treatment in a mouse model also triggers oxidative stress and initiates β-cell death through the nuclear factor erythroid-2-related factor 2 (Nrf2)/NF-κB and SAPK/JNK pathways [105]. In addition, oxidative stress could activate the NF-κB pathway to exaggerate β-cell inflammation, eventually exacerbating β-cell failure [106].

ER stress is also implicated in islet inflammation and β-cell functions. The inflammatory factors IFN-γ and IL-1β significantly downregulate sarcoendoplasmic reticulum pump Ca^{2+} ATPase 2b (SERCA2b) expression and deplete ER Ca^{2+} stores, resulting in ER stress in β-cells [85]. In isolated islets from normal mice and humans, chronic exposure to IL-6 and IL-1β can markedly deplete ER Ca^{2+} stores and trigger the ER stress response, eventually impairing glucose-stimulated insulin secretion in islet β-cells [107].

PTM also plays a vital role in this crosstalk. The pro-inflammatory factor TNF-α could facilitate SUMOylation-dependent p53 stability through the ceramide/double-stranded RNA-dependent protein kinase (PKR)/Ubc9 signaling pathway, thus inhibiting β-cell proliferation [108]. Moreover, the O-GlcNAcylation detriment may also induce ER stress, thus deteriorating β-cell mass and functionality. OGT-conditionally deficient mice in β-cells displayed elevations of ER stress and swollen ER structures, and these alterations eventually led to β-cell mass depletion [109]. The deletion of one ER transmembrane receptor protein CHOP allele alleviating ER stress was adequate to decrease high glucose and glucose intolerance in β-cell OGT-deficient mice [109]. Notably, SUMOylation can also influence oxidative stress in β-cells, as confirmed by the evidence that β-cells lacking the SUMO-binding enzyme UBC9 induce ROS accumulation, which leads to β-cell mass loss, ultimately resulting in DM occurrence [103]. As a consequence, there is a complicated feed-forward loop among oxidative/ER stress, islet inflammation, and PTM in modulating β-cell failure, indicating that the potential mechanisms of β-cell failure pathogenesis are anfractuous.

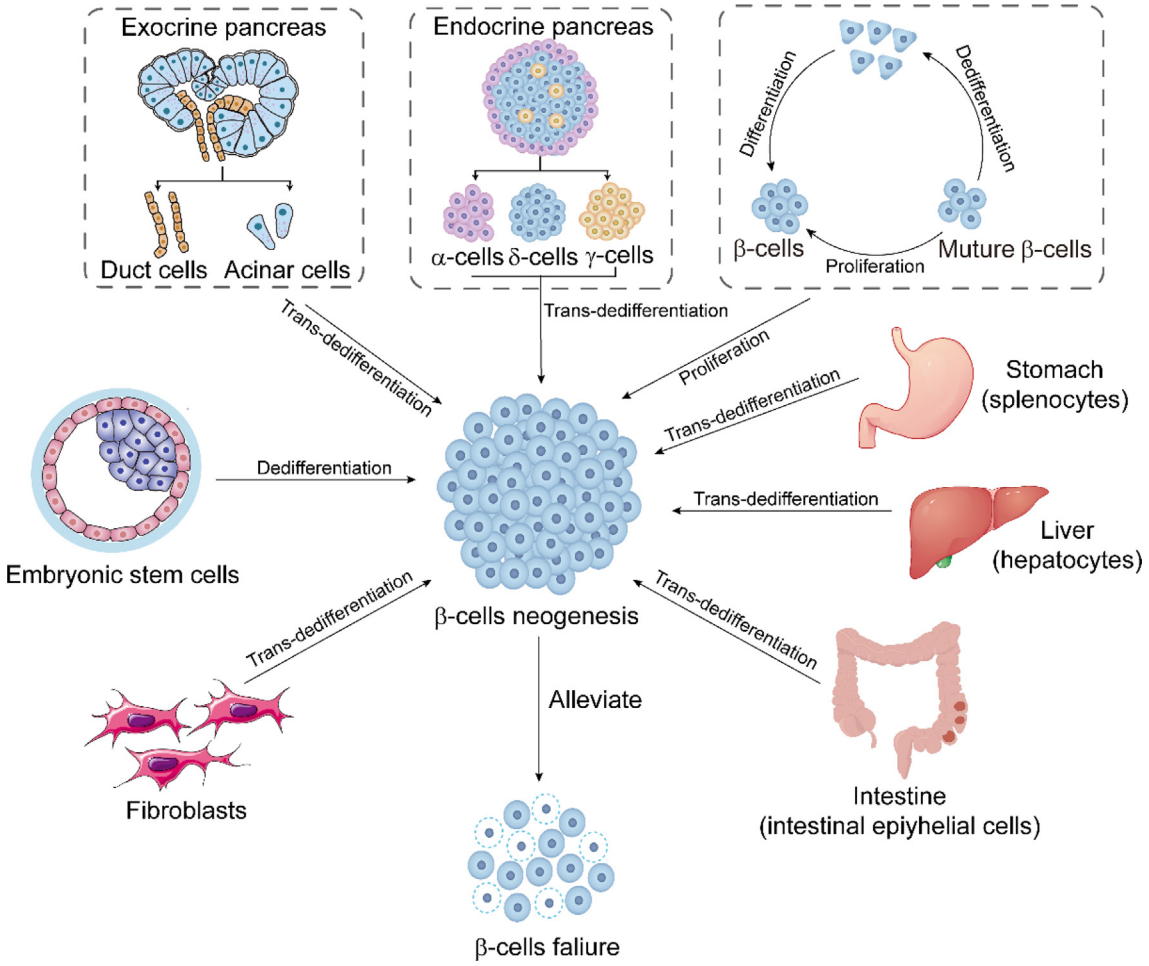

Fig. 4. Strategies of pancreatic β-cell neogenesis. The α-cells, δ-cells, and γ-cells in the endocrine pancreas and the acinar cells and ductal cells of the exocrine pancreas can be *trans*-differentiated into β-cells by reprogramming with transcription factors. The existing β-cell proliferation, inhibition of β-cell dedifferentiation, and re-differentiation of dedifferentiated β-cells into β-cells all facilitate β-cell neogenesis. Besides, stem cells and other cells such as fibroblasts, splenocytes, intestinal epithelial cells, and hepatocytes are potential sources of β-cell neogenesis.

Strategies of β-cell neogenesis

As aforementioned, pancreatic β-cell failure leads to DM pathogenesis through multiple mechanisms. Because of this, reversing β-cell loss and failure by β-cell neogenesis may be a practical approach for the expansion/restoration of β-cell mass and function. Next, we highlight the recent advances in exploring feasible strategies of β-cell neogenesis for DM therapy.

Stimulation of β-cell proliferation

The self-replicating of β-cells has gained widespread attention as the most direct way to restore pancreatic β-cell volume and mass. Conventional wisdom has long held that β-cell proliferation primarily occurs during the late embryonic and neonatal stages [110,111]. After adulthood, the turnover rate of β-cells as terminally differentiated cells decreases, and most of them are in a quiescent state, and their numbers tend to stabilize [112]. However, it has been subsequently found that the pancreas of adult animals still had the regenerative capacity to form new pancreatic lobules [113]. A study using a genetic lineage trace approach demonstrated that pre-existing β-cell proliferation in mice was the main source of β-cell regeneration under physiological and partial pancreatectomy conditions (Fig. 4) [114].

Numerous *in vivo* and *in vitro* studies have identified that serine/threonine AKT kinase, ERK/MAPK, and mammalian rapamycin complex 1 (mTORC1) signals are the critical regulators of β-cell proliferation [115,116]. AKT regulates the cyclin D1, cyclin D2, and p21 levels in a cyclin-dependent kinase (CDK) manner to achieve the islet β-cell cycle G1/S transition, thereby inducing islet β-cell proliferation, maintaining β-cell mass, and improving glucose tolerance in DM mice (Fig. 4) [117]. Substantial evidence also reveals that several molecular or epigenetic modifications can effectively enhance pancreatic β-cell proliferation and insulin release via regulating cell cycle molecules and intracellular signaling pathways [118–120]. For instance, trials in cells and mice have revealed that osteocalcin, a bone-derived hormone, could promote β-cell proliferation and enhance insulin production during development and adulthood via action on the Gprc6a receptor in a cyclin D1-dependent manner (Fig. 4) [121]. In mouse and human primary islet cells, inhibiting microRNA-7a (miR-7a) facilitates pancreatic β-cell proliferation and augments β-cell mass through activation of the mTOR signaling pathway (Fig. 4) [122].

Differentiation of stem cells into islet β-cells

Stem cells can self-renew indefinitely while retaining the potential to differentiate into multiple cell types. Therefore, β-cell neogenesis from the differentiation of stem cells may serve as an ideal and promising source for β-cell replacement therapy. Embryonic stem cells (ESCs) and adult stem cells (ASCs) are the two primary categories of stem cells [123].

ESCs, first derived from the inner cell mass of human blastocysts, can differentiate into insulin-secreting cells with a low rate of spontaneous differentiation (1-3 %) [124]. Given that, researchers tried numerous strategies to increase the differentiation rate of ESCs for inducing the differentiation of ESCs into insulin-secreting cells. Lumelsky et al. (2001) induced mouse embryonic cells to differentiate into cells that secrete insulin using a five-step approach [125], however which was subsequently proved insufficient for terminal differentiation of ESC progeny to functional β-cells [126]. D'Amour et al. (2006) developed a four-step induction approach to induce ESC differentiation into islet-secreting cells by culturing ESCs in suspension and sequentially adding activin A, fibroblast growth factor 4 (FGF4), and maintaining the growth of islet-like cells with GLP-1 or exenatide, nicotinamide adenine dinucleotide phosphate (NADP), and B27 **(**Fig. 4**)** [127]. Animal experiments demonstrated that the insulin content released by the differentiated insulin-producing cells was comparable to that of adult islets with C-peptide release. However, the immunofluorescence assay showed that the differentiated cells produced both glucagon and insulin, indicating that the insulin-secreting cells induced by this method had a low response capacity and efficiency to control blood glucose [127]. To address this concern, Blyszczuk et al. (2003) transfected mice R1 lineage ESCs with Pax4, which is an essential transcription factor for pancreatic β-cell differentiation. Immunofluorescence and ultrastructural analysis revealed that the elevation of Pax4 in mouse ESCs only increased the number of insulin-secreting cells, but not glucagon-generating cells. Moreover, immunohistological and conventional hematoxylin/eosin staining analyses demonstrated that transplanting these cells into diabetic rats markedly maintained blood glucose stability **(**Fig. 4**)** [128]. Liu et al. (2012) also proposed a two-step program to elicit ESC differentiation into insulin-secreting cells, and an enzyme-linked immunosorbent assay (ELISA) assay confirmed that these differentiated cells could secrete more insulin in response to increased blood glucose concentration, resulting in effective glycemic control **(**Fig. 4**)** [129].

ASCs are found throughout the body after embryonic development and are distributed in various tissues, e.g., the blood vessels, brain, skin, bone marrow mesenchyme, and liver. Emerging evidence indicates that cord-derived stem cells, pancreatic stem cells, and mesenchymal stem cells (MSCs) have a great potential to develop into β-cells. Especially cord blood and bone marrow MSCs were ideal cells due to their several properties, such as easy access, wide availability, high proliferation capacity, low immunogenicity, and multidirectional differentiation potential [130]. Prabakar et al. (2012) reported for the first time that human cord blood-derived mesenchymal stem cells (CB-MSCs) have the potential to differentiate into a β-cell-like phenotype and respond to glucose stimulation in both *in vitro* and *in vivo* studies **(**Fig. 4**)** [131]. Importantly, human MSC-derived trophic factors have been shown to promote the survival and function of pancreatic islets after transplantation [132].

Trans-differentiation of non-β-cells in endocrine pancreas

The endocrine pancreas contains different types of endocrine cells with distinct secretory products: α-cells (glucagon), β-cells (insulin), δ-cells (somatostatin), γ-cells (pancreatic polypeptide), and ε-cells (ghrelin). β-cells share a more remarkable similarity with other cell types in the islets. Therefore, these pancreatic non-β-cells may be another cellular source for β-cell neogenesis [133].

Pancreatic α- and β-cells have similar epigenetic characteristics, expressing a variety of identical transcription factors (e.g., PAX6, Isl1) [134] and similar hormone secretion-related components (e.g., glucokinase, ATP-sensitive K^+ channels, etc.) [135,136], and are adjacent to blood vessels, facilitating hormone release into the blood. The total number of α-cells does not decrease but rather increases after β-cell failure [137]. In a diphtheria toxin–induced selective β-cell ablation mouse model, it has been observed that spontaneous reprogramming of adult pancreatic α-cells promotes the *trans*-differentiation of α-cells into new β-cells **(**Fig. 4**)** [133,138]. Following this finding, researchers began to search for ways to "transforming α-cells into β-cells". Multiple studies have linked this "transition" to the intracellular transcription factor gene Arx [139,140]. In the mouse model of DM caused by toxin–induced β-cell depletion, specific blocking of Arx is adequate to achieve the conversion of α-cells into β-cells, leading to the argumentation of functional β-cell population **(**Fig. 4**)** [140]. Moreover, simultaneous deletion of the Dnmt1 and Arx genes in mouse pancreatic α-cells resulted in a more effective transformation of α-cells into offspring that resembled β-cells **(**Fig. 4**)** [141]. Inspiringly, in mice models, Chera et al. (2014) observed a direct conversion of α-cells into β-cells from puberty to adulthood to older stages, even a long time after β-cell loss. This transformation of α-cells was not detected before puberty. In contrast to α-cells, δ-cells in mice can be converted to β-cells before puberty (involves the joint action of FOXO1 downregulation and its downstream effectors), but not in adulthood (Fig. 4) [142]. As such, the self-programming of α- or δ-cells enables the restoration of non-β-cell-derived insulin-producing cells throughout life.

Furthermore, like α- and δ-cells, γ-cells could be converted efficiently into glucose-dependent insulin secretory cells (Fig. 4) [143]. This plasticity of γ-cells was also demonstrated in mice, where a small proportion of γ-cells expressing Ppy (2–3 %) were automatically reprogrammed to generate insulin upon β-cell destruction. Whereas, spontaneous reprogramming into insulin-producing cells from γ-cells was restricted to specific γ-cell subpopulations after β-cell ablation, and approximately one-half of the γ-cells appear to be insensitive to reprogramming **(**Fig. 4**)** [144]. Nevertheless, these studies suggest that pancreatic endocrine non-β-cells have considerable plasticity that can be *trans*-differentiated into functional β-cells under specific conditions.

Exocrine pancreas: A new source for β-cell neogenesis

The exocrine pancreas consists of acinar and ductal cells. Acinar cells were the most abundant cell type in pancreatic tissue with high plasticity and could be an attractive source of cells for β-cell neogenesis **(**Fig. 4**)** [145]. In the dabetic mouse model, it has been found that the transcription factors MAFA, PDX1, and Nsulin-secreting-neurogenin3 (NGN3) overexpression in the pancreas was capable of reprograming differentiated acinar cells into novel "β-cells" resembling endogenous β-cells in terms of size, morphology, ultrastructure, and ameliorating blood glucose level **(**Fig. 4**)** [146]. However, this differentiation presented some disadvantages, e.g., low transition efficiency (10–20 %), the scattered novel "β-cells", non-isle structures, and a fast decline in cell number [146]. Subsequently, the team increased reprogramming efficiency to 40–50 % by polyclonal co-expression of these transcription factors in acinar cells of adult mice, which induced β-cells persisting until 13 months (experimental time) to aggregate into island-like structures and that supported normal blood glucose in DM mice **(**Fig. 4**)** [147].

Ductal epithelial cells account for 30-40 % of the pancreas, and activating the differentiation of ductal epithelial cells into β-cells is another alternative route to regenerate β-cells **(**Fig. 4**)**. In human pancreatic ductal cells, ectopically expressing PAX6, MAFA, Neurog3, and PDX1 via adenoviral transfection could convert ductal cells into endocrine offspring with β-cell characteristics that could generate, handle, and release insulin in reaction to glucose **(**Fig. 4**)** [148]. The deletion of F-box and WD-40 structural domain protein 7 (Fbw7) facilitates the stabilization of NGN3, an essential regulator of endocrine cell differentiation, resulting in the reprogram-

Table 1
The preclinical and clinical agents for β-cell neogenesis.

Clinical/ preclinical agents	Model	Dosage	The mechanism of action	Effect of arginase inhibition	Refs
rSerpinB1	Mouse islets	1 μg/ml, 48 h	Up-regulates phosphorylation of proteins, including MAPK, PRKAR2B, and GSK3	Promote β-cell proliferation	[163]
	Islets from cadaveric organ donors	1 μg/ml, 48 h			
SerpinB1 mimics	Sivelestat or GW311616A	Islets isolated from wild-type mice	100 μg/ml, 48 h		
	GW311616A	C57Bl/6 male mice	2 mg/kg/day, 2 weeks		
	Sivelestat	Transplanted human islets under the kidney capsule of mice	300 μg/kg/day, 14 days		
GLP-1 RAs	Exendin-4	Transplanted human islets under the renal capsule of mice	24 nmol/kg/day, 4 weeks	Stimulates calcineurin/NFAT signaling and proliferation-promoting factors	Stimulate β-cell proliferation in transplanted juvenile [175]
		Human islets	2.5 nM, 10 nM, 4 days	Activate mTOR and Wnt/GSK3/β-catenin pathways	Promote β-Cells growth and proliferation [174]
		Rat islets	1, 2.5, and 5 nM, 4 days		
		Human ductal cells	10 nM, 30 days	—	Induce human pancreatic ductal cell differentiation to insulin secretive cells [176]
	Liraglutide	Tamoxifen-inducible β cell-specific GLP-1R-KO mouse model	200 μg/kg/twice day, 2 weeks	Induce α-cell PC1/3 and GLP-1 expression mediated by GLP-1R	Induce α-cells conversion to functional β-like cells [177]
		Islets from a human donor	100 nM, 12 h (RNA), 24 h (protein)		
		Beta-TC-6 cells	1000 nM, 48 h	Stimulate PI3K-dependent AKT pathway and inhibited caspase-3 activation	Promote β-cell survival and suppress β-cells apoptosis [178]
		Mouse model of T2DM BKS.Cg-m^{+}/$^{+}$Lepr db/BomTac	1000 μg/kg/day, 2 weeks		
	Semaglutide				
	75 adult participants with T2DM	1.0 mg (0.25, 0.5, 1.0 mg escalated) or placebo, once weekly, 12 weeks.	—	Improve β-cell function and glycemic control	[179]
	Lixisenatide	DM NSG RIP-DTR mice engrafted with islets from a single human donor	50, 150, and 500 μg/kg, twice weekly	—	Increaseβ-cell survival and enhanced β-cell function, restoring normoglycemia levels [180]
	Dulaglutide	Participants with T2DM	Dulaglutide 1.5 mg/week, dulaglutide 0.75 mg/week, or metformin ≥ 1500 mg/day;	—	Improve β-cell function [181]
DPP-IV inhibitors	Saxagliptin	HFD/STZ–Induced DM Rats	1 mg/kg, 12 week	It might be by enhancing SDF-1α to actuate AKT, β-catenin as well as proliferation-associated proteins, c-myc, and cyclin D1	Promote β-cells growth and proliferation [186]
		INS-1 832/13 cells	100 nM, 48 h		
	Vildagliptin	Alloxan–induced DM Fischer rats	5 mg/kg body weight/day, 30 days	—	Promote β-Cells growth and proliferation [188]
Artemisinins	Mouse β-cell line Min6	10 μM, 72 h	Targeting GABAA receptor signaling to inhibit Arx expression.	Induction of α-cells conversion to functional β-like cells	[139]
Salidroside	Mice	100 mg/kg, 5 weeks	Decrease NOX2 expression and inhibit the JNK-caspase 3 apoptotic cascade; Activate AMPK-AKT to suppress FOXO1 and recover PDX1 nuclear localization	Promote β-cell proliferation and survival	[195]
	Min6 Cells	50 μM, 3 days			
Curcumin derivative	STZ–induced DM rats	150 mg/kg, 40 days	—	Promote β-cell proliferation, improve insulin synthesis and secretion	[200]
	Isolated rat islets	10 μM, 24 h	Inhibition of the JNK pathway, up-regulation HO-1, TCF7L2, and GLP-1 expressions.	Promote β-cell proliferation, improve insulin synthesis and secretion	[201]

Table 1 (*continued*)

Clinical/ preclinical agents	Model	Dosage	The mechanism of action	Effect of arginase inhibition	Refs
Curcumin	STZ–induced DM rats	170 mg/kg, three times weekly, 28 days	Inhibition of the NF-κB phosphorylation exerts immunosuppressive effects on pro-inflammatory cytokines	Promote β-cell proliferation, improve insulin synthesis and secretion	[203]
Allicin (the active component of garlic)	STZ–induced DM rats	8 mg/kg/day, 16 mg/kg/day, 30 days	–	Prevent the failure of β-cell	[204]
Garlic extract	STZ–induced DM rats	500 mg/0.5 mL/kg b.wt, 8 weeks	–	Change the expression of NGN3, PDX1, and MAFA genes in pancreas	[205]
GABA	Wild-type mice	250 μg/kg/week, 2 months	Induce Arx decrease and Pax4 ectopic expression in α-cells	Induction of α-cells conversion to functional β-like cells	[194]
	Transplanted human islets Immunodeficient mice were transplanted with human islet	250 μg/kg, 14 days 250 μg/kg/day, 1 month			
	INS-1 cells and isolated mouse islets	100 μM, 20 to 24 h	Activate Ca^{2+}/PI3K/AKT pathways	Promote β-cell proliferation and survival	[190]
	Transplanted human islets into immunodeficient NOD-scid-γ mice	6 mg/mL, 5 weeks	Activate PI3K/AKT and CREB-IRS-2 pathways	Promote β-cell proliferation and modulate glucose homeostasis	[191]

ming of adult pancreatic duct cells to β-cells. Notably, these newly formed β-cells resemble endogenous islet β-cells with similar morphology and histology, express β-cell function-related essential genes, and secrete insulin following glucose stimulation (Fig. 4) [149].

Inhibition of β-cell dedifferentiation and transformation

β-cell dedifferentiation is one of the key reasons for β-cell failure in diabetes, which has been clarified in a series of β-cell lineage tracing experiments, diabetic mouse model experiments, and clinical DM patients [19,22,150,151]. In T2DM patients, dedifferentiation but not apoptosis is one of the major causes of β-cell mass loss–induced cell failure and dysfunction of insulin secretion [22]. Therefore, early intervention to rescue the dedifferentiated β-cells is practical to improve β-cell failure. Excitingly, dedifferentiated β-cells can be re-differentiated to mature islet β-cells with secretory functions (Fig. 4) [152].

Several signaling pathways and factors have been identified to be engaged in suppressing β-cell dedifferentiation or facilitating dedifferentiated β-cells to re-differentiate into β-cells. (a) The activation of the NOTCH pathway induces β-cell proliferation and dedifferentiation, while inhibition of the NOTCH downstream regulator hairy and enhancer of split (HES)-1 by short hairpin RNA (shRNA) could decrease β-cell dedifferentiation in isolated human islet cells (Fig. 4) [153]. Likewise, suppressing HES1 expression in expanded β-cell-derived (BCD) cells using HES1 shRNA is also adequate to elicit re-differentiation of BCD cells [154]. (b) The TGF-β pathway is activated in expanded human islet cells. Blocking the TGF-β pathway by suppressing TGF-β receptor 1 (TGFBR1, ALK5) activation could prevent the dedifferentiation of cultured islet cells (Fig. 4) [155]. (c) Also, the dedifferentiation of BCD cells is correlated with activation of the WNT pathway through β-catenin translocation into the nucleus. Inhibition of the β-catenin expression causes BCD cell growth arrest and redifferentiation [156]. (d) Moreover, miR-375 overexpression promotes the re-differentiation of human BCD into functional insulin-producing cells via targeting the PDPK1-AKT pathway and GSK3 expression [157].

Additionally, lineage-tracing studies in severe diabetic KATP-GOF mice revealed that β-cells that had de-differentiated into neurogenic protein 3-positive and insulin-negative cells could re-differentiate into mature neurogenic protein 3-negative, insulin-positive β-cells after long-term treatment with slow-release insulin pellets to lower blood glucose [19]. Recent *in vivo* and *in vitro* investigations indicate that long-term excess nutrient supply can trigger the loss of β-cell differentiated characteristics such as glucose-stimulated insulin secretion, and this process is reversible [158,159]. Therefore, body weight loss in humans can restore first-phase insulin secretion in early T2DM patients [158,159].

Besides, β-cell transformation to endocrine cells could also induce islet β-cell failure (Fig. 4). In *ex vivo* mature insulin-containing β-cells derived from diabetic animals and patients, the loss of their identity and *trans*-differentiation of β-cells into other pancreatic endocrine cell types (α- and δ-cells) have been observed [20–22,160]. Inactivating the transcription factor Arx can block β-cell *trans*-differentiation to α-cells, which has a beneficial effect on enhancing β-cell mass (Fig. 4) [21,140,161]. Notably, with the development of single-cell sequencing and molecular biology, CD49a as a specific protein with high expression in the β-cell population was identified by the transcriptional profiles of thousands of human cells differentiating from β-cells *in vitro*, which may offer an insightful perspective for investigating human β-cell differentiation [162].

Targeting β-cell neogenesis for DM therapy

Pancreatic β-cells can be neoplastic through multiple pathways, providing a promising avenue for treating DM. In recent years, researchers have discerned several synthetic drugs and phytochemical agents for β-cell regeneration (Table 1). Here, we highlight the recent research advances of preclinical and clinical agents that target β-cell neogenesis for the treatment of DM.

SerpinB1

Serine protease inhibitor B1 (SerpinB1) is a conserved serine protease inhibitor secreted by the liver. Together with its analogs, it has been demonstrated to augment pancreatic β-cell proliferation in multiple species, including zebrafish, mice, and humans [163]. The phosphoproteomic analysis revealed that SerpinB1, recombinant human SerpinB1 (rSerpinB1), and SerpinB1 mimics could promote β-cell proliferation through the upregulation of phosphorylation of proteins, including PRKAR2B, MAPK, and glycogen synthase kinase-3 (GSK3) [163]. When insulin signaling is disrupted in the liver, FOXO1 could facilitate serpin B1 expression in a non-cell-independent manner, thus contributing to β-cell proliferation [164]. According to a clinical study conducted in Egyptian type 2 diabetic patients, the genotype AA of SerpinB1 single-nucleotide polymorphism (SNP) rs15286 is closely correlated with amelioration of β-cell function and blood glucose homeostasis, while the G allele tends to be a "risk allele" damaging glycemic control [165], indicating the potential implication of SerpinB1 for DM therapy.

GLP-1 and GLP-1 receptor agonists

Glucagon-like peptide 1 (GLP-1), encoded by the proglucagon gene, is an incretin excreted from intestinal L-cells that facilitates β-cell insulin secretion in a glucose-dependent pathway during the postprandial period [166]. Numerous studies have convinced us that GLP-1 plays vital roles in β-cell neogenesis, including stimulating β-cell proliferation and apoptosis, and re-differentiation of dedifferentiated β-cells [167,168]. GLP-1 exerts these functions by combining with abundantly expressed GLP-1 receptors on the β-cell membrane [169]. Active GLP-1 with a short half-life ($T_{1/2}$, 2 mins) is quickly degraded by dipeptidyl peptidase IV (DPP-IV) in plasma, which greatly limits its clinical application of GLP-1 [170]. In this regard, GLP-1 receptor agonists (GLP-1 RAs) were exploited with prolonged half-lives relative to endogenous GLP-1.

Currently, there are six commercially available GLP-1 RAs for treating T2DM, namely exenatide, liraglutide, semaglutide, albiglutide, dulaglutide, and lixisenatide [171]. Among them, exenatide, isolated from lizard saliva, is the first Food and Drug Administration (FDA)-granted GLP-1 RA to treat DM with 53 % homology to human GLP-1 [172], and has a half-life of approximately 2.4 h following subcutaneous administration twice daily [173]. Among humankind and rat islets, it regulates the mTOR and glycogen synthase kinase-3 (GSK-3)/β-Catenin pathways to promote human β-cell growth and proliferation [174]. In diabetic mice grafted with human juvenile islets, it could rejuvenate β-cells by stimulating β-cell proliferation and neogenesis via upregulating calcineurin/activated T-cell nuclear factor signaling and the expression of pro-proliferation factors (FOXM1, CCNA1, and NFATC1) [175]. Furthermore, co-treatment with exenatide and activin A (ActA) could stimulate the differentiation of human pancreatic ductal cells into insulin-producing cells, which facilitated blood glucose control in STZ–induced diabetic mice [176].

Apart from exenatide, liraglutide has been found to promote the abundance of β-cell-like genes in α-cell subclusters of human islets [177]. In a tamoxifen–induced β-cell-specific GLP-1R-KO mouse model, liraglutide treatment increased bihormonal insulin$^+$ and glucagon$^+$ cells at the islet periphery in a GLP-1R–dependent manner [177]. In obese db/db mice models and mouse βTC-6 cells, therapy with liraglutide increased β-cell survivability and resisted apoptosis by stimulating AKT phosphorylation and blocking caspase-3 activation [178]. In a randomized, double-blind and placebo-controlled trial, weekly semaglutide exposure (12 weeks) substantially ameliorated β-cell function and hyperglycemia among T2DM individuals [179]. In diabetic mice engrafted with borderline human islet mass, lixisenatide administration significantly enhanced β-cell viability and improved β-cell function, in turn restoring normoglycemia levels [180]. Dulaglutide [181] and albiglutide [182] could also ameliorate glucose management by improving β-cell function among T2DM subjects. However, the action mechanism of these GLP-1 receptor agonists in improving β-cell function to achieve β-cell neogenesis deserves additional investigation.

Overall, GLP-1 and GLP-1 receptor agonists exhibit great potential for increasing insulin secretion via stimulating β-cell neogenesis for DM therapy [183]. Whereas, multiple side effects, e.g., vomiting, diarrhea, nausea, and dizziness, accompany the clinical application of these drugs. As such, the use of combination therapy (e.g., liraglutide in combination with metformin) regimens is often recommended to treat T2DM [184].

DPP-IV inhibitors

DPP-IV inhibitors are FDA-approved prescription medicines that treat T2DM by suppressing the degradation of incretin hormones such as GLP-1 and glucose-dependent insulin-like peptides [185]. Extensive research has demonstrated that the specific inhibition of DPP-IV promotes β-cell neogenesis, which partially contributes to therapeutic effects on DM. Some DPP-IV inhibitors, for example, vildagliptin and saxagliptin, are anti-diabetic agents that have been confirmed to be linked to β-cell neogenesis. In HFD/STZ–induced DM rats and INS-1 cells, saxagliptin administration promotes islet β-cell proliferation via activating AKT, β-catenin, c-myc, and cyclin D1 [186]. In a randomized, double-blind and placebo-controlled clinical study, saxagliptin reduced postprandial glucagon concentration and improved β-cell function in post-meal and fasted conditions of T2DM patients [187]. Also, vildagliptin administration for 30 days significantly induces β-cell neogenesis, enhances serum insulin content, and ameliorates β-cell function in the alloxan–induced T1DM rat [188]. Notably, the combination of DPP-IV inhibitors and metformin for DM therapy has been underway in a clinical study (see, e.g., https://www.clinicaltrials.gov, NCT02407899).

GABA

γ-Aminobutyric acid (GABA), generated by decarboxylation of the glutamate by glutamate decarboxylase (GAD) in β-cells, contributes to β-cell neogenesis via interacting with membrane receptors on islet cells [189]. Current studies indicate that GABA promotes β-cell neogenesis through the Ca^{2+}/PI3K/AKT, CREB-IRS-2 signaling axis, and transcription factor NGN3.

In INS-1 cells and isolated mouse islet cells, GABA promoted β-cells proliferation and protected β-cells from apoptosis via activating the Ca^{2+}/PI3K/AKT pathway, thus enabling β-cell regeneration to reverse β-cells failure [190]. In diabetic immunodeficient NOD-scid-γ mice transplanted with a suboptimal mass of human islets, GABA activates calcium-dependent signaling pathways via its receptors, which in turn activate the PI3K-AKT and CREB-IRS-2 signaling pathways to promote the proliferation of transplanted β-cells and maintain glucose homeostasis [191].

During pancreas morphogenesis, the transcription factor NGN3 has been reported to specify the endocrine cell lineage. Upon induction of NGN3 expression, a network of diverse transcription factors involving Pax4 and Arx drives endocrine precursors to distinct endocrine cell destinies [192]. Arx and Pax4 are essential for the differentiation of glucagon-expressing α-cells and insulin-secreting β-cells, respectively [193]. A study revealed that either *in utero* development or adulthood, Pax4 ectopic expression or Arx inactivation evokes terminal differential α-cell rejuvenation and converts them to functional β-cells [140]. Excitingly, the NGN3-regulated endocrine developing system is awakened by the prolonged GABA treatment, which downregulates Arx and Pax4 expression in α-cells, ultimately promoting the transformation of α-cells into functional β-like cells to repeatedly reverse chemically induced diabetes [194]. Moreover, in the 3D culture of human islets or immunodeficient mice transplanted with human islets under their renal capsule, the treatment with GABA also leads to loss of α-cells and a concomitant increase in β-like cell counts, indicating that the α- to β-like cell conversion process also exists in humans [194]. Inspiringly, clinical trials are currently underway to evaluate the therapeutic effects of GABA in T1DM (see, e.g., https://www.clinicaltrials.gov, NCT04375020).

Phytochemical agents

Apart from synthetic drugs, several phytochemical compounds also display a promotive effect on β-cell neogenesis and thereby can be potentially used for diabetes treatment. For instance, salidroside, a natural antioxidant derived from the pharmaceutical herb rhodiola rosea, has been reported to enhance β-cell number and proliferation while inhibiting apoptosis in HFD–induced diabetic mice [195].

Curcumin, a phenolic compound derived from the rhizome of Curcuma longa, has been found to possess anti-oxidative [196], anti-inflammatory [197], anti-tumor [198], and anti-diabetic [199] properties. Notably, in rats with STZ–induced DM, curcumin derivatives have been shown to reduce plasma glucose levels and increase insulin and c-peptide concentrations by mitigating the failure of β-cells to maintain their numbers in the Langerhans islets [200]. This mechanism is believed to involve the upregulation of gene expression of transcription factor 7-like (TCF7L2), heme oxygenase-1 (HO-1), and glucagon-like peptide-1 (GLP-1) [201]. In rat pancreatic β-cells, curcumin was also found to enhance the electrical activity of β-cells through stimulation of the volume-regulated anion channel (VRAC) [202]. Similarly, in STZ–induced diabetic mice, curcumin has exhibited anti-diabetic properties by promoting the regeneration of β-cells through its immunosuppressive effects on proinflammatory cytokines (IFN-γ, IL-6, IL-1β and IL-2) by suppressing the phosphorylation of NF-κB [203].

Artemisinin, an approved anti-malarial agent extracted from *Artemisia annua*, has been shown to promote insulin release in α-cells and impair α-cells identity, as well as increase β-cell mass in human islets [139]. Mechanistically, it activates GABA signaling in α-cells by targeting Gephyrin, which leads to the translocation of Arx across the nucleus into the cytoplasm, resulting in the suppression of Arx expression [139].

Besides, it has been discovered that allicin, the active compound in garlic, serves as a protective agent against β-cell failure and effectively elevates blood insulin levels in type 1 diabetic rats [204]. Al-Adsani et al. (2022) revealed that the administration of garlic extract (GE) significantly upregulated the expression of crucial transcript factors (NGN3, PDX1, and MAFA) involved in β-cell differentiation within the pancreas, resulting in enhanced insulin secretion in STZ–induced diabetic rats [205].

Overall, the results from preclinical *in vitro* and *in vivo* studies show that the use of phytochemical agents can promote β-cell regeneration, improve β-cell homeostasis, increase β-cell quality and function, and reduce β-cell failure, thereby offering great promise for DM therapy. In addition, phytochemical agents have less toxicity and side effects than commercially available antidiabetic drugs. They are low in cost but high in availability, making them an excellent alternative to combat diabetes and its related complications [206]. However, the drawbacks of phytochemical reagents, including low aqueous solubility, poor absorption resulting in low bioavailability, and an unpleasant taste [207], compromise their potential use for DM therapy. Presently, there is attention being given to the nanoencapsulation delivery system, in which phytochemical compounds encapsulated in biocompatible nanomaterials with enhanced solubility and bioavailability are delivered to targeted β-cells to protect them from STZ-induced inflammation and apoptosis [208].

Future research avenues and limitations

(a) Over the past few years, we have seen considerable progress in the induction of human pluripotent stem cell differentiation into functional β-like cells for large-scale production of β-cells, which holds great potential for DM therapy [209,210]. Presently, clinical trials are undergoing safety and efficiency tests in DM patients [211]. However, there are still some inescapable challenges for stem cell-based DM therapies. For example, the strong immune responses in the host-immune rejection of the transplanted stem cell-derived β-cells, and autoimmunity against β-cells lead to the loss of primitive β-cells. Although adopting the patient's hiPSC-derived β-cells minimizes immune exclusion, the combination of stem cell-derived β-cell neogenesis and immune tolerance elicitation could improve long-term therapeutic outcomes, especially in T1DM sufferers. Many researchers are currently attempting to induce immune tolerance using animal models and have made initial progress, but it is still far away from preclinical testing. Moreover, a rigorous and standardized preclinical test is necessary to assess the function and potential defects of stem cell-differentiated β-cells for recipients, including the expression profiles of defined mature β-cell markers, the insulin secretory response to glucose, the capacity of insulin-secreting cells suppressing insulin secretion upon hypoglycemia, the short- and long-term physiological responses of patients (immune system, metabolism, body weight, heart function, etc.), as well as the sustainability and stability of transplanted stem cell-derived β-cells [211]. Additionally, determining the cell dose required for the therapy of DM patients, removing undifferentiated stem cells effectively, and eliminating any tumor formed by the implanted cells to mitigate safety concerns are also crucial for the widespread application of stem cells-derived functional β-like cells for DM therapy [211].

(b) Non-β-cells, including fibroblasts, keratin-forming cells, hepatocytes, gastrointestinal tract cells, neural cells, and islet α-cells, have been explored in preclinical studies to be converted into β-cells via *in vivo* reprogramming (Fig. 4) [212]. Most of these cells are abundant and easy to obtain. The transcription factors PDX1, NGN3, neurogenic differentiation factor (NeuoD1), MAFA, and Pax4 have been verified to play essential roles in the growth and development of islet β-cells. Therefore, these cells can be *trans*-differentiated into islet β-like cells by selectively transfecting the above transcription factors and adding cytokines or small molecules. For instance, the co-expression of PDX1, NGN3, and MAFA by viral vector transduction could reprogram the antral

stomach epithelial cells into insulin$^+$ cells, and the acinar cells towards β-cells [212]. Nevertheless, the reprogramming protocols are based on viral vector-mediated transduction of the reprogramming factors that often elicit a robust inflammatory response, which raises clinical safety concerns. The efficient and specific delivery system of reprogramming factors to target tissues or cells is also challenging, especially when multiple or sequential deliveries of transcription factors are required. In addition, many *trans*-differentiated β-like cells do not have complete β-cells function, which might compromise their efficiency and potential. Accordingly, further studies are warranted to address how to deliver reprogramming genes to target specific tissues or cells in an efficient, precise, and safe manner.

(c) Current β-cell neogenesis protocols involving stem cell differentiation and transformation of non-β-cells to produce β-like cells are inefficient and unstable, and the yield and maturity of the induced-generated β-like cells are still low for clinical needs. Therefore, improving the efficiency of β-cell regeneration and producing enough mature functional β-like cells for clinical requirements is of prime importance. Using synthetic drugs or extracted natural compounds to stimulate the neogenesis of islet β-cells, might be feasible for β-cell neogenesis. Whereas, the notable disadvantages of drug-stimulated pancreatic β-cell regeneration, including the lack of clarity of drug action mechanisms, uncertain inflammatory response, and excessive metabolic stress, which may result in oncogenic consequences. Consequently, it is imperative to further explore the action mechanism of drug-stimulated β-cell regeneration, and exploit novel drugs with potent efficiency and low cytotoxicity.

(d) Genetic factors also serve as an essential driver for β-cell failure. Recently, Bevacqua et al. (2021) used CRISPR-based targeting technology effectively to mutate the protein-coding exons of PDX1 and KIR6.2 (ATP-sensitive K^+ channel subunit) in primary human β-cells, causing an acute depletion of pancreatic β-cell regulators with concomitant impairment of β-cell regulation and function [213]. Also, CRISPR/Cas9-based genome editing has been applied to manipulate pancreatic β-cell function in human stem cell-derived insulin$^+$ cells [214] and β-cell lines [215]. With further development, CRISPR/Cas9 technology may pave the way for DM therapy (especially T1DM) through gene editing of β-cell failure-related non-coding and coding variants. However, a large number of challenges, including ethical issues, the requirement for efficient delivery systems, off-target effects, and safety concerns, still remain unsolved.

Concluding remarks

Taken together, β-cell failure as a key driver for the initiation and development of DM is modulated by genetic susceptibility, ER stress, oxidative stress, islet inflammation, and protein modifications. A large body of experimental and clinical studies have indicated that disrupting β-cell failure by β-cell neogenesis offers a promising approach for defeating DM. We highlight the current strategies of β-cell neogenesis, including stimulation of β-cell proliferation, inhibition of β-cell dedifferentiation, promoting the differentiation of stem cells into islet β-cells, and *trans*-differentiation of non-β-cells in the endocrine and exocrine pancreas. Moreover, a variety of synthetic drugs and natural compounds that target β-cell neogenesis have been developed and exhibited promising results for DM therapy. Whereas, there still exist several unsolved questions and some challenges that need to be addressed before β-cell neonatal strategies can be fully translated from the preclinical findings into clinical applications.

CRediT authorship contribution statement

Fanglin Niu: Investigation, Writing – original draft, Writing – review & editing, Visualization. **Wenxuan Liu:** Investigation, Writing – original draft, Writing – review & editing, Visualization. **Yuanyuan Ren:** Writing – review & editing, Visualization. **Ye Tian:** Writing – review & editing, Visualization. **Wenzhen Shi:** Writing – review & editing, Visualization. **Man Li:** Writing – review & editing, Visualization. **Yujia Li:** Writing – review & editing, Visualization. **Yuyan Xiong:** Writing – review & editing, Conceptualization, Supervision. **Lu Qian:** Writing – original draft, Writing – review & editing, Conceptualization, Supervision.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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