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Review

Functions and Mechanisms of Diabetes-Linked Transcription Factors

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Abstract

Transcription factors are significant regulators of gene expression in most biological processes related to diabetes, including beta cell (β-cell) development, insulin secretion and glucose metabolism. Dysregulation of transcription factor expression or abundance has been closely associated with the pathogenesis of type 1 and type 2 diabetes, including pancreatic and duodenal homeobox 1 (*PDX1*), neurogenic differentiation 1 (*NEUROD1*), and forkhead box protein O1 (*FOXO1*). Gene expression is regulated at the transcriptional level by transcription factor binding, epigenetically by DNA methylation and chromatin remodelling, and post-transcriptional mechanisms, including alternative splicing and microRNA (miRNA). Recent data indicate a central role for transcription factors in pancreatic β-cell failure in the context of systemic insulin resistance and chronic inflammation. Therapeutic modulation of transcription factor abundance via gene therapy, small-molecule pharmacology, and epigenetic therapies holds great promise for β-cell restoration and metabolic normalisation. However, further clinical translation will require targeted delivery to appropriate tissues, minimising off-target effects and ensuring long-term safety. This review focuses on the involvement of pancreatic β-cells and transcription factors in diabetes development and their therapeutic implications, intending to develop and consolidate a basis for further research in this area and for the treatment of diabetes in the future.

Keywords: diabetes; pancreatic transcription factors; epigenetic therapy; chromatin remodeling; metabolic dysfunction; insulin resistance; hepatic gluconeogenesis; lipid metabolism; inflammatory responses; islet cell types

1. Introduction

Diabetes is a chronic metabolic disorder characterised by persistently high blood glucose levels over a relatively long period [1]. Due to a paradigm shift in lifestyle, aging of the population, and increasing rates of obesity, the global prevalence of the disease has increased phenomenally within the last two decades [1]. In 2021, there were 529 million (95% uncertainty interval [UI] 500–564) people living with diabetes worldwide, and the global age-standardised total diabetes prevalence was 6.1% (5.8–6.5). Prevalence has been rising more rapidly in low- and middle-income countries than in high-income countries. The study in the Lancet predicted that between 2021 and 2050, the global age-standardised total diabetes prevalence is expected to increase by 59.7% (95% UI 54.7–66.0), from 6.1% (5.8–6.5) to 9.8% (9.4–10.2), resulting in 1.31 billion (1.22–1.39) people living with diabetes in 2050 [2]. Diabetes leads to serious long-term complications, which are broadly categorised as macrovascular or microvascular. Macrovascular complications affect large vessels and result in cardiovascular events such as heart attack and stroke [3]. Microvascular complications affect smaller vessels and cause diabetic retinopathy, which affects the eyes, diabetic nephropathy, and diabetic neuropathy, which affects the nerves [4]. These complications reduce the quality of life of patients with diabetes and contribute to other health conditions, including an increased risk of infection and foot conditions [4,5]. Diabetes is a life-threatening condition requiring constant management and treatment [5].

Transcription factors (TFs) are a class of proteins that bind specific DNA sequences to modulate the transcriptional activity of genes. They regulate the expression of genes at the transcription stage and, therefore, play a critical role in switching genes on and off and controlling the extent of expression. Transcription factors may function as activators that stimulate transcription or repressors that block this process [6]. This regulatory system is essential for many cellular processes, including development, differentiation, and environmental responses. The binding of transcription factors to DNA at the promoter or enhancer regions is a crucial way RNA polymerase is either enabled or prevented from transcribing a gene to produce the corresponding mRNA [3]. TFs are therefore central to maintaining cellular identity and function, with consequences of aberrant function observed in diseases such as cancer and some genetic disorders such as diabetes, congenital hypothyroidism, and syndromes such as Rett syndrome and Waardenburg syndrome, all considered to be linked with mutations that affect specific transcription factor genes [7].

TFs connect cellular signalling pathways to major metabolic functions such as insulin secretion and beta cell (β-cell) survival along with immune responses. Pancreatic and duodenal homeobox 1 (*PDX1*) functions by triggering insulin gene transcription while simultaneously maintaining β-cell survival through increasing expression of anti-apoptotic genes such as *BCL2*. The signal transducer and activator of transcription 4 (*STAT4*) protein triggers proinflammatory cytokine generation such as IFN-γ in type 1 diabetes which leads to β-cell damage by activating autoimmune responses [8] NF-κB becomes active because of ER stress [9]. Nuclear respiratory factor 1 (NRF1) is a transcription factor that regulates mitochondrial function through transactivation of genes encoding components of the respiratory chain and factors involved in mitochondrial biogenesis, which are required for efficient insulin secretion from pancreatic β-cells [4]. Perturbation of NRF1 diminishes ATP levels and impairs glucose-stimulated insulin secretion, and thus, is an essential component of β-cell function and survival [4]. Other transcription factors that promote mitochondrial function and, consequently, glucose metabolism affecting insulin secretion include peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), the levels of which are diminished in the setting of type 2 diabetes (T2D)-controlled immune responses via modulation of inflammatory and cell stress responses, thereby connecting metabolic health to immune function [10].

TFs play important roles in diabetes management by regulating metabolic pathways that influence metabolic processes, such as lipid metabolism and insulin sensitivity. For instance, forkhead box protein O1 (*FOXO1*) is a major transcription factor that controls hepatic gluconeogenesis; inhibition of this factor reduces glucose overproduction and increases sensitivity to insulin. In contrast, sterol regulatory element-binding protein 1c (*SREBP1c*) controls lipogenesis in the liver and its overactivity contributes to hepatic steatosis and hyperlipidaemia. Thus, the specific targeting of these factors by selective inhibitors or modulators may offer alternative valid therapeutic approaches to metabolic dysfunction with fewer side effects. The complex mechanisms developed in relation to these TFs interact with signalling pathways such as PI3K/protein kinase B (Akt) and AMP-activated protein kinase (AMPK). A deeper understanding of these factors will lead to the development of safer and more effective therapies against diabetes [1].

This review outlines the knowledge gaps related to the role and mechanism of TFs in pancreatic islet cells, with particular emphasis on pancreatic β-cells which are at the centre of insulin production and glucose regulation in diabetes. Emphasis is placed on the importance of incorporating approaches that connect molecular biology with clinical knowledge and therapeutic applications. Making such connections may open new avenues of research into diabetes and result in effective treatment of patients. Furthermore, interdisciplinary investigations possess the capacity to emphasise the contributions of non-β-cells that affect diabetes risk, thereby enhancing the understanding of the underlying mechanisms of the disease.

2. Diabetes-Linked TFs

TFs are determinants of developmental stages in pancreatic β-cells and functional aspects of viability throughout life. Dysregulation of the developmental process leads to the pathogenesis of diabetes and its complications [5]. Table 1 (Ref. [11–16]) presents some of the most relevant TFs involved in β-cell differentiation and insulin expression: *PDX1*, NK6 homeobox 1 (*NKX6.1*), v-Maf musculoaponeurotic fibrosarcoma oncogene homolog A (*MAFA*), neurogenic differentiation 1 (*NEUROD1*), and forkhead box A2 (*FOXA2*), which participate in glucose homeostasis [5,11]. For instance, disruption of the *PDX1*-a gene, which is implicated in the process of β-cell differentiation and insulin gene transcription, promotes β-cell impairment, which reduces insulin secretion and contributes to the development of T2D. Analogous to this, *NKX6.1*, which is required for β-cell maturation and expansion, its disturbed expression causes loss of β-cell identity with impairment in insulin biosynthesis [17]. Although *MAFA* is crucial for glucose sensing and insulin secretion, its downregulation favours glucotoxicity, leading to β-cell dysfunction and increased vulnerability to oxidative stress. Similarly, impairment of *NEUROD1* severely affects the differentiation and viability of β-cells [18]. In contrast, dysregulation of *FOXA2* is disadvantageous to β-cell function and survival and contributes to the worsening of diabetes pathogenesis [19]. These TFs constitute interwoven networks whose perturbation results in many defects in β-cell function, insulin secretion, and glucose homeostasis (See Fig. 1 for the roles of major TFs in diabetes pathogenesis).

Additionally, Hepatocyte Nuclear Factor 4α (*HNF4*α) functions as a key regulator in β-cell glucose detection and insulin production beyond the TFs previously discussed. *HNF4*α gene mutations cause Maturity-Onset Diabetes of the Young 1 (MODY1) through progressive β-cell dysfunction. Reduced *HNF4*α activity in T2D leads to impaired insulin secretion following glucose stimulation because glycolytic enzyme expression levels decrease, particularly for solute carrier family 2 member 2 (*SLC2A2*) (glucose transporter type 2 (*GLUT2*)) and glucokinase (*GCK*) [15]. The zinc finger transcription factor Krüppel-like factor 11 (*KLF11*) is found at reduced levels in diabetic islets which leads to increased oxidative stress and apoptosis such as B-cell lymphoma 2-associated X protein (BAX) expression. The *KLF11* transcription factor attaches to the insulin (INS) promoter, from which its absence halts insulin production and triggers β-cell dedifferentiation [16]. The genetic and functional heterogeneity of transcriptional regulators during diabetes development becomes evident through these TFs.

As well as the TFs involved in pancreatic development and differentiation, other TFs have been implicated in diabetic complications. These include CCAAT enhancer binding protein beta (*CEBPB*), Jun proto-oncogene (*JUN*), and Fos proto-oncogene (*FOS*), which have all been implicated in vascular calcification (VC). High-glucose-induced activation of *CEBPB* upregulates miR-32–5p [20], downregulates the protective regulator of vascular smooth muscle cell differentiation GATA binding protein 6 (*GATA6*), and promotes VC in T2D [20]. This could provide an example of how TFs interact with diabetic vascular pathology. Other TFs implicated in hepatic gluconeogenesis are *FOXO1* and phosphoenolpyruvate carboxykinase (PEPCK) [18,20]. Dysregulation of *FOXO1* promotes gluconeogenic gene expression and perpetuates a state of insulin resistance and hyperglycaemia, with PEPCK, a transcriptional target of *FOXO1*, being a key mediator of glucose overproduction [20].

Some TFs have opposing functions in diabetes. For example, mothers against decapentaplegic homolog 3 (*SMAD3*) and *PDX1* are representative of the bifunctional nature of TFs in diabetes, with *SMAD3* inhibiting insulin transcription and promoting β-cell dysfunction via the transforming growth factor beta (TGF-β)/*SMAD3* pathway activity, whereas *PDX1* activates insulin gene expression and is required to maintain β-cell function [18]. In contrast, in type 1 diabetes (T1D), *DEXI* (Dexamethasone-induced transcript 2) mediates anti-inflammatory responses in β-cells, whereas suppressor of cytokine signaling 1 (*SOCS1*) regulates cytokine signalling [18]. Signal transducer and activator of transcription (STAT) and activator protein (AP-1) further exacerbate T1D by driving proinflammatory responses and chromatin remodelling, contributing to β-cell destruction [21].

TFs contribute to T1D and T2D through shared but distinct mechanisms, suggesting that their roles in the pathogenesis of diabetes are multi-layered. While *PDX1* and *NEUROD1* are essential in both T1D and T2D because of their essential roles in β-cell-specific functions [5], others, such as *FOXO1* and PEPCK, significantly contribute to T2D through metabolic pathways [22]. Elucidation of the molecular dynamics of these TFs may point toward specific therapies aimed at protecting β-cells, restoring glucose homeostasis, and possibly reducing diabetic complications.

2.1 Pancreatic Islet TFs

Pancreatic islet TFs are among the most important regulators of β-cell development, survival, and function because they regulate insulin gene expression. *PDX1* is the major transcription factor (TF) that commits pancreatic progenitors to the insulin-producing β-cell lineage, thus providing functional identity to the cells [19,23]. *PDX1* positively interacts with its expression, activating the transcription of critical β-cell-specific genes, including insulin. Similarly, *MAFA* plays a vital role in glucose sensing within β-cells by modulating calcium signalling to amplify the response to glucose stimuli, an essential event for efficient insulin release [19,24]. Moreover, *MAFA* can preserve β-cell identity and function, thereby maintaining optimal performance against metabolic stress. *NEUROD1* also promotes β-cell terminal differentiation by inducing TFs such as *PDX1* [17,19]. This cooperative interaction increases insulin production and the formation of storage granules, resulting in functional maturation of β-cells.

Dysregulation of the action of the TFs *NKX6.1* and the regulatory factor X (RFX) family is highly implicated in diabetes pathogenesis. *NKX6.1* maintains β-cell identity and controls genes required for cell cycle progression, supporting β-cell proliferation and insulin gene expression [25]. Mutations in these mechanisms lead to aberrant glucose metabolism and insulin secretion. Conversely, Harris *et al.* (2021) [26] indicated that the RFX family of TFs, notably RFX3, RFX4, and RFX7, have been implicated in the development of cilia and central nervous system functions. However, they are also involved in glucose homeostasis. Their dysregulation can interfere with cell signalling pathways and reduce insulin secretion [25]. *NKX6.1* and RFX factors are both critical in β-cell-cell function, with *NKX6.1* playing a central role mainly in proliferation and RFX factors in insulin secretion.

Specific TFs control insulin biosynthesis and secretion at both levels. For example, Hasnain *et al.* (2014) [17] showed that interleukin (IL)-22 could rejuvenate glucose-induced insulin secretion by inhibiting endoplasmic reticulum stress caused by proinflammatory cytokines. This illustrates how TFs maintain β-cell function through complex, yet distinct pathways, each in response to a particular physiological setting of proliferation or secretion, a schematic representation of the sequential contribution of TFs to β-cell differentiation is shown in Fig. 2 (Ref. [17,19,25,27–29]).

2.2 TFs Influencing Insulin Responsiveness in Target Tissues

TFs in insulin-responsive tissues, such as the liver, skeletal muscle, and adipose tissue, are critical for maintaining glucose and lipid homeostasis. Dysfunctional activity seriously underlies the development of insulin resistance and T2D [30].

FOXO1 is an essential modifier of hepatic glucose metabolism that mediates gluconeogenesis in response to metabolic and carbohydrate signalling. Stojchevski *et al.* (2024) [31] demonstrated that in a model of induced insulin resistance, increased *FOXO1* activity leads to higher hepatic glucose output through the upregulation of gluconeogenic genes, thereby exacerbating hyperglycaemia. More importantly, the interaction of *FOXO1* with a key insulin signalling component, insulin receptor substrate 2 (IRS2), further supports the role of *FOXO1* in perpetuating insulin resistance and disturbing glucose metabolism during chronic states [22,32].

Peroxisome proliferator-activated receptor gamma (PPARγ) is responsible for lipid metabolic pathways and insulin sensitisation [31]. It promotes the differentiation of preadipocytes into adipocytes, enhances the accumula-

Table 1. Roles, mechanisms, and effects of key TFs linked to diabetes pathogenesis.

Transcription factor	Function	Mechanism	Diabetes type	Dysregulation outcome	References
PDX1	β-cell differentiation, insulin gene expression	Activates β-cell-specific genes	T1D, T2D	β-cell failure, reduced insulin secretion	[11,12]
MAFA	Glucose sensing, insulin production	Modulates calcium signalling for glucose-stimulated insulin secretion	T2D	Loss of β-cell identity	[12]
FOXO1	Gluconeogenesis regulation	Promotes gluconeogenic gene expression	T2D	Insulin resistance, hyperglycemia	[12]
NF-κB	Mediates inflammation	Regulates pro-inflammatory cytokines	T1D, T2D	β-cell destruction, chronic inflammation	[13]
SREBP1c	Lipogenesis regulation	Induces genes involved in lipid synthesis	T2D	Hyperlipidemia, hepatic steatosis	[14]
HNF4α	Regulates glucose-responsive genes	Activates *SLC2A2*, *GCK*	T1D, T2D, MODY1	Impaired insulin secretion	[15]
KLF11	Suppresses β-cell apoptosis	Represses pro-apoptotic *BAX*	T2D	β-cell loss, hyperglycaemia	[16]

TFs, Transcription factors; *PDX1*, pancreatic and duodenal homeobox 1; *MAFA*, v-Maf musculoaponeurotic fibrosarcoma oncogene homolog A; *FOXO1*, forkhead box protein O1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; *SREBP1c*, sterol regulatory element-binding protein 1c; *HNF4*α, Hepatocyte Nuclear Factor 4α; *KLF11*, Krüppel-like factor 11; T1D, type 1 diabetes; T2D, type 2 diabetes; MODY1, Maturity-Onset Diabetes of the Young 1; *SLC2A2*, solute carrier family 2 (facilitated glucose transporter), member 2; *GCK*, glucokinase; *BAX*, B-cell lymphoma 2-associated X protein.

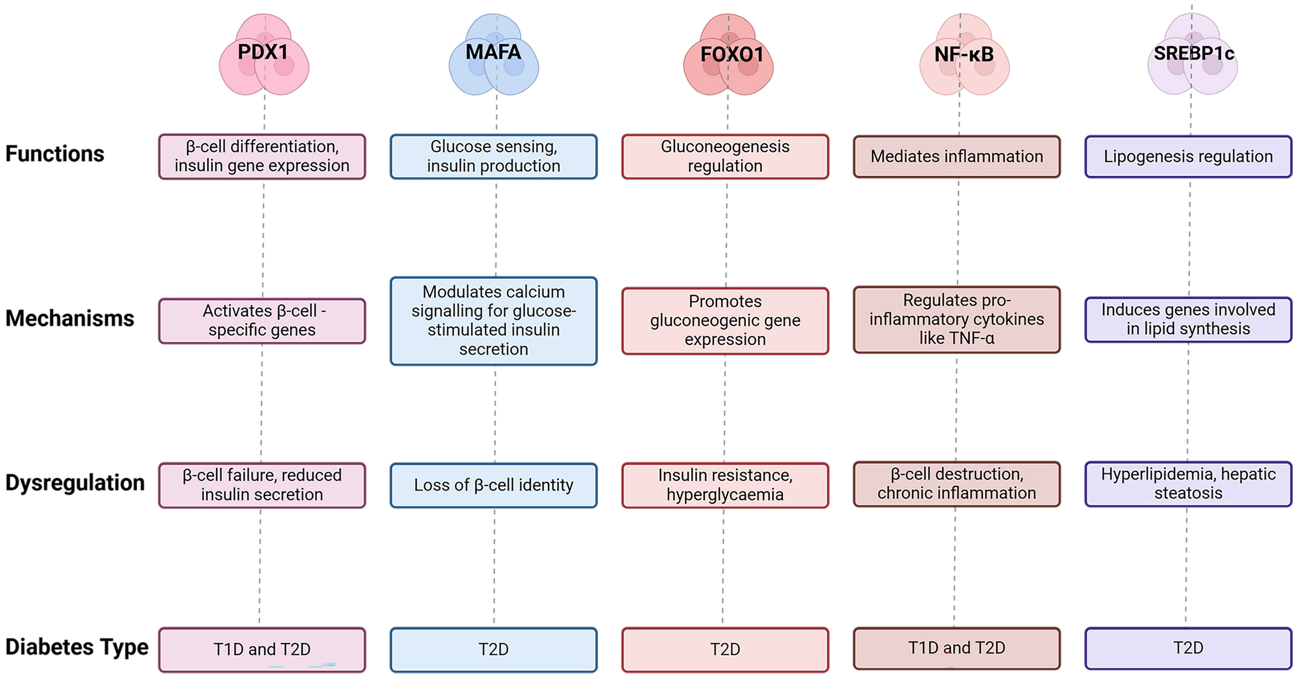

Fig. 1. The role(s) of the major TFs involved in the pathogenesis of diabetes, including *PDX1*, *MAFA*, *FOXO1*, NF-κB, and *SREBP1c*, include their function, mechanism of action, consequence of dysregulation, and type of diabetes with which each is associated with T1D and T2D. Created in BioRender.com. Simpson, A. (2025) https://BioRender.com/h37q534.

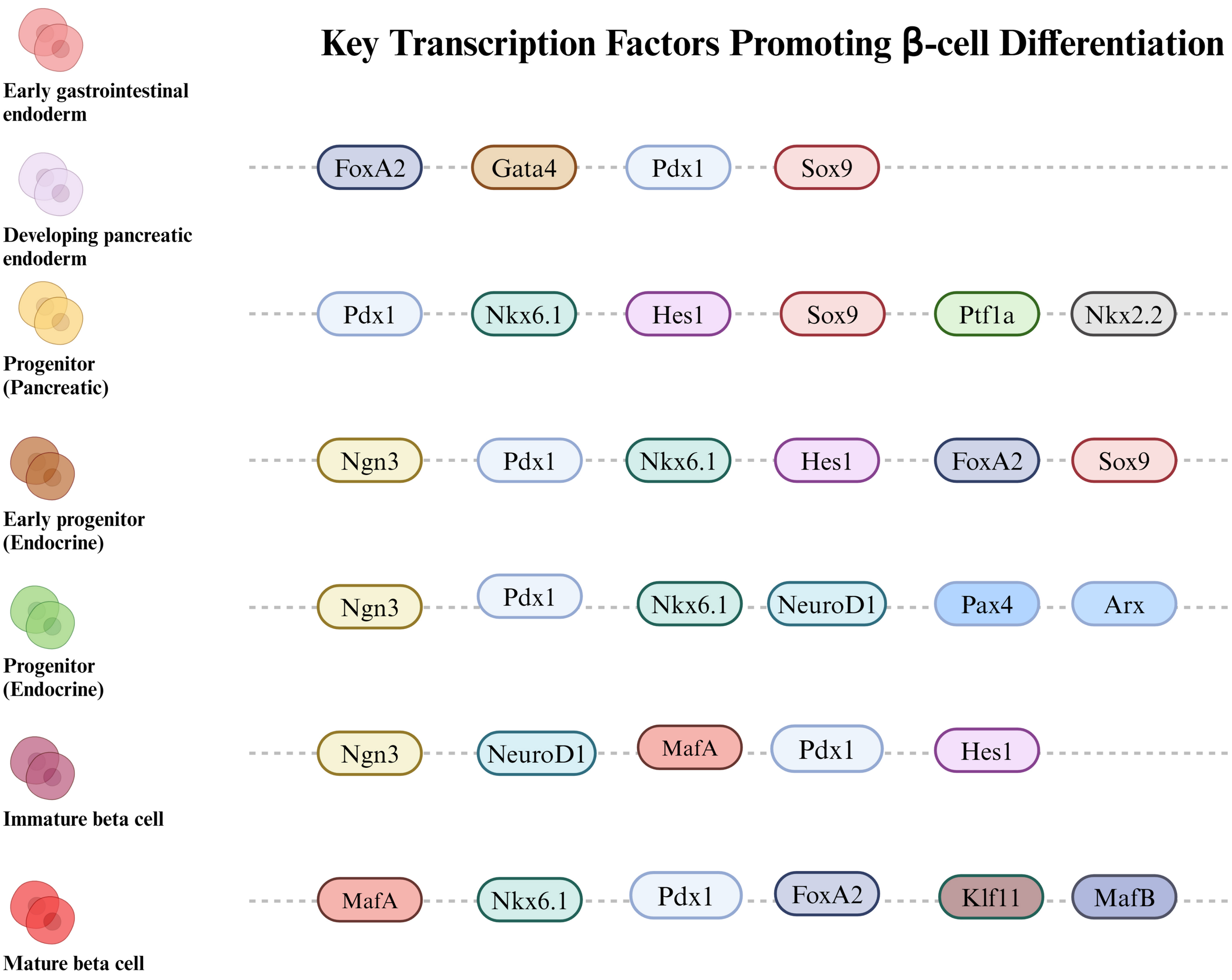

Fig. 2. Schematic representation of how various TFs sequentially contribute to the β-cell differentiation pathway from early gastrointestinal endoderm to mature β-cells. The TFs forkhead box A2 (*FoxA2*), GATA binding protein 4 (*Gata4*), *Pdx1*, and SRY-box transcription factor 9 (*Sox9*) initiate general differentiation programs at early stages [19,27]. When the pancreatic endoderm develops, *Pdx1*, NK6 homeobox 1 (*Nkx6.1*), hairy and enhancer of split 1 (*Hes1*), *Sox9*, pancreas transcription factor 1 subunit alpha (*Ptf1a*), and NK2 homeobox 2 (*Nkx2.2*) [25,28]. Specification of the endocrine lineage involves TFs including, but not limited to, neurogenin 3 (*Ngn3*), *Pdx1*, *Nkx6.1*, *Hes1*, and *FoxA2* [29]. Early endocrine progenitors would later express *Ngn3*, neurogenic differentiation 1 (*NeuroD1*), paired box 4 (*Pax4*), and aristaless-related homeobox (*Arx*) for endocrine commitment [17,19]. *NeuroD1*, *MafA*, *Pdx1*, and *Hes1* regulate immature β cells. Maintenance of mature β-cell function and insulin secretion depends on other factors, including *MafA*, *Nkx6.1*, *Pdx1*, *FoxA2*, *Klf11*, and v-Maf avian musculoaponeurotic fibrosarcoma oncogene homolog B (MafB) [17,29]. Thus, all of these TFs act in concert to develop and maintain functional β-cells in glucose homeostasis Created in BioRender.com. Simpson, A. (2025) https://BioRender.com/d30c608.

tion of stored lipids, and increases fatty acid uptake. By further modulating the insulin signalling pathway, PPARγ regulates glucose homeostasis and metabolic responses in white adipose tissue; thus, PPARγ regulates lipid storage and general metabolic health [10,31].

SREBP1c, through Akt signalling, is an effective inducer of lipogenic genes in the insulin response, which requires nuclear trafficking in the endoplasmic reticulum followed by proteolytic processing for nuclear translocation to activate target gene expression [33,34]. In insulin-resistant states, however, where this is impaired, apart from disturbing glucose homeostasis, *SREBP1c* unleashes uncontrolled lipogenesis, leading to hyperglycaemia, hyperlipidaemia, and hepatic steatosis. Insulin resistance is characterised by metabolic dysfunction and further drives the development of diabetes.

Carbohydrate-responsive element-binding protein (ChREBP) is a glucose-responsive transcription factor that interacts specifically with carbohydrate response elements, which mediate the primary transcriptional activity of genes encoding glycolytic enzymes in response to high glucose availability [33]. This transcription factor induces glycolytic and lipogenic genes in response to a high intake of carbohydrates in the liver, including liver pyruvate kinase (LPK), which is required for the appropriate use of glucose and deposition of triglycerides [33,35]. The state of its phosphorylation controls its activity, that is, its DNA-binding ability and subsequent transcriptional activity. This marks the final role attributed to TFs, such as ChREBP, in maintaining blood glucose levels.

These interactions in insulin-responsive tissues are integrated into complex networks that regulate glucose and lipid metabolisms. For example, insulin, through Akt, activates *SREBP1c* but inhibits *FOXO1* in the liver, and this reciprocal regulation maintains the balance between glucose production and lipogenesis [32,35]. Insulin signalling in skeletal muscle regulates the expression of TFs responsible for glucose uptake and fatty acid oxidation, thus playing a critical role in maintaining insulin sensitivity. Thus, TFs such as PPARγ and uncoupling protein 1 (UCP-1) influence lipid accumulation, energy expenditure, and inflammatory responses in adipose tissue, all of which are integral to systemic insulin resistance [31].

Recent studies have focused on how some TFs, including anterior open (Drosophila ETS transcription factor) (AOP), FOXO, and pointed (Drosophila ETS transcription factor) (PNT), interact in hepatic and adipose tissues to change the metabolic rate and, as a result, longevity [10,36]. In the skeletal muscle, factors such as fibroblast growth factor 19 (FGF19) stimulate glucose uptake and lipid metabolism through signalling pathways initiated by AMPK and sirtuin 1 (SIRT1), which control PGC-1α and fibronectin type III domain-containing protein 5 (FNDC-5) to modulate irisin secretion [10]. This transcriptional network illustrates how tissue-specific TFs cooperate to maintain insulin sensitivity and ameliorate metabolic disorders.

Insight into such interactions may provide a general understanding of possible therapeutic approaches that target TFs to improve insulin resistance and T2D. Such tissue-specific actions and systemic interactions of regulators may reveal unique ways to restore metabolic imbalance.

2.3 TFs in Inflammation and Immune Responses

TFs are critical regulators of gene expression related to the inflammatory and immune responses. They are molecular switches that drive the expression of genes essential for various immune processes [13]. β-cell dysfunction, chronic inflammation, and insulin resistance are implicated in the dysregulation of these TFs.

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a common mediator of inflammation and β-cell destruction in autoimmune diseases and T2D [13]. Typically, this is mediated by the activation of NF-κB in response to pro-inflammatory cytokines, such as TNF-α, which upregulates genes that induce apoptosis, leading to the death of β-cells. Saturated fatty acids enhance the inflammatory response through NF-κB activation and drive β-cell apoptosis [13]. Such an inflammatory milieu also impairs insulin signalling and further compromises β-cell function to promote the development [13,17]. Therefore, NF-κB plays a critical role and is an essential target for describing the relationship between inflammation and β-cell dysfunction [13].

The STAT family of TFs, particularly *STAT4*, have emerged as critical regulators in immune responses implicated in the pathogenesis of diabetes [8,21]. Induction by cytokines, such as IL-12, triggers *STAT4*-dependent transactivation of IFN-γ, orchestrating TH1 immune responses [21]. Further induction of *STAT4* activity due to diabetes promotes the production of proinflammatory cytokines, thus contributing to insulin resistance and chronic inflammation [21]. In contrast, deficiencies in *STAT4* have been demonstrated to reduce such injurious effects, and thus have emphasised an essential role in the pathogenesis of T1D and T2D.

Interferon Regulatory Factors (IRFs) modulate the expression of chemokines in the context of chronic inflammation associated with diabetes and, by doing so, prolong the infiltration of immune cells into the sites of inflammation, creating a continuous inflammatory environment that contributes to insulin resistance and metabolic dysregulation [10,37]. Abnormal IRF function disrupts the balance between pro- and anti-inflammatory mediators, characterising chronic inflammation in T1D and 2 diabetes [37,38]. Therefore, the regulation of chemokines and inflammatory responses places IRFs in a critical role in the development of diabetes. *IRF5* and AP-1 further exacerbate diabetic inflammation. The activation of *IRF5* leads to M1 macrophage polarisation, which results in enhanced TNF-α and IL-6 production within adipose tissue [39]. Activation of AP-1 by IL-1β in β-cells leads to decreased expression of *PDX1* and *MAFA*, which results in faster dedifferentiation [40]. The use of antisense oligonucleotides to target *IRF5* resulted in decreased islet inflammation in non-obese diabetic mice (NOD mice), which demonstrates therapeutic possibilities [39].

Chronic inflammation mediates a positive feedback loop by inducing several TFs that in turn promote β-cell destruction. Indeed, pro-inflammatory cytokines such as IL-1β and TNF-α repress the expression of crucial β-cell identity genes, including insulin 2 (INS2) and SLC2A2, leading to β-cell dedifferentiation [10,13]. Additionally, TGF-β signalling initiates ST2 expression and directs the maturation of group 2 innate lymphoid cells (ILC2) which connects transcription factor-driven cytokine signaling with immune balance in adipose tissue and systemic metabolic control [41]. In this process, there is a significant downregulation or change in the mRNA levels of essential TFs, such as *PDX1* and *NKX6.1* [5,11,13]. Dedifferentiation of β-cells highly contributes to impaired glucose metabolism and inflammation; hence, NF-κB is involved in this process.

Anti-inflammatory treatments decrease β-cell dysfunction, although they do not completely restore the expression of identity markers. Such effects to fully reverse β-cell dedifferentiation are limited, and suggest a role for targeted therapies in modulating TFs that may dampen the inflammatory response and protect β-cell function in diabetes.

2.4 TFs and Pathways Modulating β-cell Dysfunction and Apoptosis

β-Cell dysfunction and apoptosis are central events in the pathogenesis of diabetes, driven by the disturbed expression of crucial TFs that are sensitive to cellular stress [9]. *FOXO1* and C/EBP homologous protein (CHOP) are significant regulators of β-cell stress response and apoptosis. *FOXO1*, induced by endoplasmic reticulum (ER) stress and exposure to fatty acids, drives the expression of pro-apoptotic genes, leading to β-cell apoptosis [9,42]. Importantly, *FOXO1* controls CHOP expression, thus regulating these two factors through a common apoptotic pathway. β-Cell death under stress was suggested to involve *FOXO1*, and its inhibition reduced apoptotic markers, thereby improving β-cell survival following its dual role in adaptation or dysfunction [9].

CHOP is an essential mediator of apoptosis after ER stress, and while necessary to maintain cellular homeostasis, it becomes deleterious after stress if it is highly activated [9]. This further complicates the understanding of β-cell dysfunction because of the interconnected nature of the transcriptional regulation of proapoptotic signals. *FOXO1* and CHOP are essential for regulating β-cell apoptosis, and their dysregulation has been implicated in the pathogenesis of diabetes [9].

Another key player is represented by JNK and its corresponding JNK pathway, which is implicated in the β-cell ER stress response. Active JNK induces the expression of TFs such as activating transcription factor 3 (*ATF3*), which transactivates pro-apoptotic genes [43]. Although JNK activation is initially an adaptive reaction, under chronic hyperglycaemia and glucotoxicity conditions, its continuous activation leads to β-cell dysfunction and apoptosis [9,43]. It is also associated with impaired insulin sensitivity in the liver, creating a vicious cycle caused by increased β-cell strain and accelerated β-cell exhaustion [43].

By its very nature, hyperglycaemia impairs the activity of key TFs, further promoting β-cell dysfunction. For example, high glucose levels induce hypoxia-inducible factor 1-alpha (HIF-1α), which initiates inflammatory and pro-apoptotic pathways that adversely affect β-cell viability [37]. Hyperglycaemia disrupts the average balance of TFs that control insulin secretion, which reduces insulin biosynthesis and increases β-cell stress [37]. This differential expression underscores the multifaceted regulatory mechanisms by which TFs accomplish cellular homeostasis under normal conditions and contribute to metabolic stress and the consequent dysfunction [37,38].

Other critical oxidative stress pathways, induced by activating certain TFs, also induce β-cell apoptosis [38]. Pro-inflammatory cytokines induce NF-κB, which, in turn, upregulates the expression of inducible nitric oxide synthase (iNOS) and further generates peroxynitrite, a potent mediator of β-cell death [13,37]. The persistent activation of the β-cell NLRP3 inflammasome increases endoplasmic reticulum stress and oxidative damage which triggers cell death and worsens β-cell loss in diabetes [44]. At the same time, oxidative stress triggers pro-apoptotic genes such as BH3-interacting domain death agonist (*BID*) and Cell death-inducing DFFA-like effector A (*CIDE-A*) and inhibits anti-apoptotic molecules such as B-cell lymphoma 2 (Bcl-2), thus tilting the balance toward apoptosis [37]. Additionally, JNK signalling also tips the balance by downregulating the promoter activity of Bcl-2 to amplify the apoptotic response to oxidative stress [42,43].

Through interacting and regulatory networks, these TFs determine the balance between survival and apoptosis of β-cells [9]. Besides accelerating the deterioration in β cell function, their dysfunction underlines the urgent need for focused therapeutic approaches to restore transcriptional homeostasis in islets from individuals with diabetes.

The connection between glucose metabolism (Fig. 3A), ER stress (Fig. 3B), reactive oxygen species (ROS) (Fig. 3C), NF-κB (Fig. 3D), and cytokines (Fig. 3E) reveals how insulin production along with β-cell survival remains balanced across healthy conditions and disease states (Fig. 3).

2.5 TFs in Non-Beta Islet Cells and Diabetic Complications

The development of diabetes involves contributions from non-beta islet cells through the action of transcription factors that include aristaless-related homeobox (*ARX*) in α-cells and haematopoietically-expressed homeobox (Hhex) in δ-cells [45]. The transcription factor *ARX* initiates and promotes glucagon production and increased levels of *ARX* aggravate hyperglucagonemia in T2D [45]. Hhex regulates somatostatin secretion, modulating insulin-glucose crosstalk [46]. Islet paracrine signaling becomes disrupted when TFs are deregulated, which reveals therapeutic targets across multiple cell types [45].

Specific TF pathways are implicated in the development of diabetic complications including retinopathy, nephropathy, and cardiovascular diseases [4]. Increased vascular endothelial growth factor (VEGF) levels due to HIF-1α activation under hyperglycemia initiates angiogenesis in diabetic retinopathy [47]. NF-κB along, with TGF-β/*SMAD3*, initiates fibrosis in diabetic nephropathy through the activation of genes related to inflammation and fibrosis [18,48]. The suppression of *GATA6* by *CEBPB* in vascular smooth muscle cells regulates vascular calcifica-

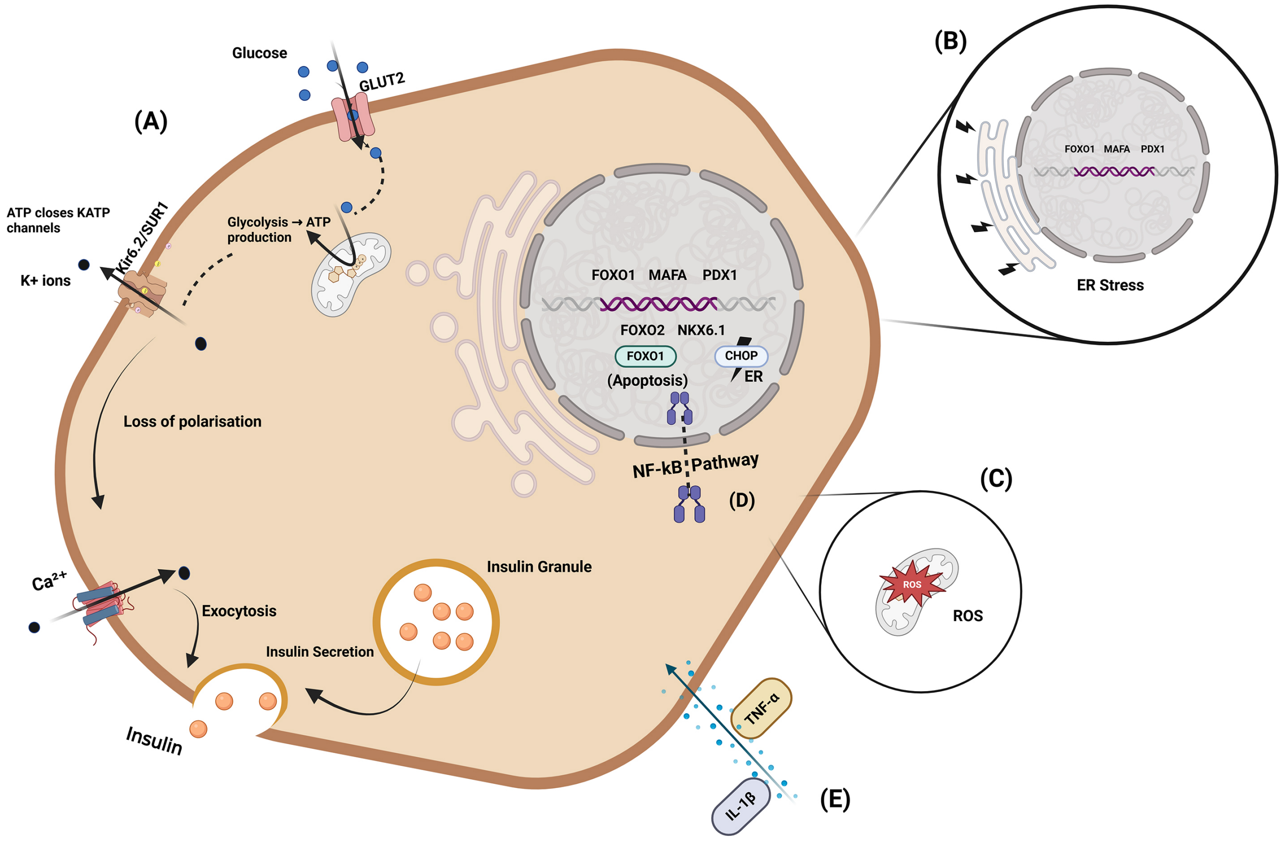

Fig. 3. Integrated pathways regulating insulin production and β-cell adaptation under metabolic stress and inflammation. This schematic illustrates a pancreatic β-cell, highlighting key pathways: (A) Glucose transporter type 2 (GLUT2) transporters help glucose enter pancreatic β-cells where glycolysis produces ATP that leads to the closure of ATP-sensitive potassium channel (KATP) channels and depolarizes the cell membrane to open voltage-gated calcium channel (VGCC)s. Insulin granule release occurs through calcium entry which also activates *PDX1* and *MAFA* transcription factors to boost insulin gene expression. (B) Endoplasmic reticulum (ER) Stress Pathways: ER stress triggers C/EBP homologous protein (CHOP) activation which suppresses *PDX1* protein levels to block insulin gene transcription. (C) Reactive oxygen species (ROS) Modulation: The regulation of *FOXO1* function through ROS alters stress responses and impacts the lifespan of β-cells. (D) NF-κB Pathway: NF-κB becomes active because of ER stress and inflammatory processes resulting in both apoptotic cell death and impaired β-cell function. (E) Inflammatory Cytokines: TNF-α and interleukin (IL)-1β (shown in the diagram) work together with stress signals to increase damage to β-cells. The interaction between glucose metabolism (A), ER stress (B), ROS (C), NF-κB (D), and cytokines (E) shows how insulin production and β-cell survival balance under both normal and disease states (see Sections 2.1, 2.4). Created in BioRender.com. Simpson, A. (2025) https://BioRender.com/o94m886.

tion during atherosclerosis [22]. These pathways demonstrate how transcription factors can operate in distinct or unique ways, as well as share mechanisms in the development of diabetes and its subsequent complications.

3. Mechanisms of Transcription Factor Action

TFs represent one of the most essential classes of gene expression regulators and are significant players in cellular homeostasis in response to metabolic and environmental signals. Their mode of action involves direct interaction with DNA at specific promoter or enhancer regions, recruitment of coactivators and corepressor proteins, and modification of chromatin structures [49]. TFs are targets of highly sophisticated regulation at multiple levels, including transcriptional regulation (including DNA methylation and histone remodelling), post-transcriptional regulation (such as microRNA (miRNA)-mediated control), and post-translational modifications (including phosphorylation and ubiquitination) [50]. These regulatory mechanisms dynamically control the critical pathways essential for β-cell function, glucose metabolism, and inflammation, which are intrinsic to the pathogenesis of diabetes, a comparison of transcriptional modifications and their effects on TFs associated with diabetes is provided in Table 2 (Ref. [13,14,34,36,51–53]) [9,37,42,43,50]. These mechanistic studies provide critical insights into the role of TFs in health and disease, thereby offering possible therapeutic opportunities for treating diabetes.

Table 2. Comparison of transcriptional modifications and their effects on TFs associated with diabetes.

Modification types	Target TFs	Effect on activity	Relevance to diabetes	References
Phosphorylation	*FOXO1*	Suppresses nuclear activity, promotes cytoplasmic retention	Reduces β-cell apoptosis, improves glucose metabolism	[14]
Ubiquitination	EZH2	Targeted for degradation	Reduces inflammation, enhances β-cell survival	[51]
Acetylation	*PDX1*	Enhances DNA binding and transcription	Promotes β-cell differentiation and insulin production	[34,52]
Sumoylation	*FOXO1*, NF-κB	Stabilises protein and enhances inflammatory gene expression	Exacerbates chronic inflammation in diabetes	[13,53]
Deacetylation	SIRT1	Promotes anti-inflammatory response	Reduces oxidative stress and insulin resistance	[36]

EZH2, enhancer of zeste homolog 2; SIRT1, sirtuin 1.

3.1 Transcriptional Mechanisms

TFs linked to diabetes control essential cellular functions by interacting with their target DNA-binding motifs, including positive regulatory domain III/positive regulatory domain I (PRDIII/PRDI) and AP-1 [50]. For instance, MafB activates the AP-1 motif, stimulating the cytokine promoter activity of genes such as interferon β1 (*IFNB1*), and represses over-activation at the positive regulatory domain III/positive regulatory domain I composite sequence (P31CS) motif, thereby hindering the cell from hyperactivity. Paired box 4 (*PAX4*) regulates the immune response, cell cycle, and DNA damage response pathways. It is one of the most important TFs that enhances neogenesis and survival of β-cells under stress [54]. Post-translational modifications further modulate TF activity. The *PDX1* promoter experiences DNA hypermethylation due to hyperglycaemia which leads to its expression silencing and increases the rate of β-cell dedifferentiation [55]. Chromatin remodelling complexes further modulate the activity of TFs by changing the chromatin conformation in a way that can be permissive or nonpermissive to DNA accessibility and subsequent gene transcription [49]. The dynamic nature of gene expression regulated by these complexes involves acetylation and deacetylation of histones in response to metabolic signals [56]. In addition, TFs such as *FOXO1* and *PDX1* are highly regulated through feedback mechanisms in the balance of glucose metabolism, insulin signalling, and inflammatory responses via Akt/PI3K and mitogen-activated protein kinase (MAPK), which are important for β-cell function and metabolic homeostasis [14,34].

3.2 Post-Translational Mechanisms

Generally, post-translational modifications are essential for fine-tuning the activity of the TFs involved in diabetes. Phosphorylation is likely the most important process in post-translational mechanisms. Phosphorylation is expected the most important step in these processes. *FOXO1*, for instance, undergoes insulin-induced phosphorylation at sites such as Thr-24, Ser-256, and Ser-319, which prevents its translocation into the nucleus and causes its retention in the cytoplasm, thereby hindering its transcriptional activity [14]. Furthermore, the phosphorylation of Ser-256 may be subjected to additional phosphorylation events that allow interaction with nuclear export proteins. Similarly, phosphorylation affects TFs such as *SREBP1c*, where signalling pathways regulate its expression via factors such as specificity protein 1 (Sp1) and liver X receptor (LXR), modulating the transcription of target genes [14].

Ubiquitination affects the stability of TFs. For example, the E3 ligase F-box/WD repeat-containing protein 7 (FBW7) targets enhancer of zeste homolog 2 (EZH2) for proteasomal degradation [14]. Lower levels of FBW7 in T1D favour the stability of EZH2 and enhance β-cell inflammation and apoptosis [14]. In contrast, degradation of EZH2 by FBW7 upregulates the transcription factor zinc finger and BTB domain-containing protein 16 (ZBTB16), favouring insulin signalling and mitochondrial function, thus underlining the FBW7-EZH2-ZBTB16 axis as a therapeutic target [14].

Under ER stress *FOXO1* becomes Sumoylated which maintains its nuclear localisation and increases the activity of pro-apoptotic genes such as *CHOP* [9,57,58]. The study reveals that sumoylation of NF-κB homologs including Dorsal reduces Toll/NF-κB signaling which shows how sumo modifications regulate inflammatory transcription factor function [57]. Metabolic stressors activate modifications which lead to transcriptional dysregulation [58]. For example, the diabetes-associated variant paired box 4 Arg129Trp variant (*PAX4*R129W) abrogates this protective function by reducing adaptive gene expression, such as cyclin D3, and simultaneously upregulating pro-apoptotic factors, including cyclin-dependent kinase inhibitor 2A (CDKN2A), thus negatively affecting β-cell proliferation and survival [54,59]. Upregulation of CDKN2A (p16INK4a), promotes cell-cycle arrest. Increased expression of CDKN2A mRNA is a transcriptomic marker of clinically aggressive meningiomas, which is also consistent with a more general role for this gene in regulation of disease-associated proliferation [60].

Table 3. Summary of epigenetic modifications that influence TFs and their clinical implications in diabetes.

Modification	Target gene/factor	Impact on gene expression	Clinical implication	References
DNA methylation	NF-κB	Reduces transcriptional activity	Suppresses pro-inflammatory responses, reduces β-cell dysfunction	[50]
Histone acetylation	*PDPX1*	Enhances chromatin openness	Improves insulin secretion and β-cell function	[71]
Histone methylation	IL-6	Increases inflammatory gene expression	Exacerbates chronic inflammation and insulin resistance	[70]
Non-coding RNAs	PPARγ	Regulates lipid metabolism gene expression	Reduces lipid accumulation, improves insulin sensitivity	[31]
lncRNA-mediated modification	TGF-β pathway	Impacts TFs indirectly	Alters β-cell stress responses and metabolic regulation	[56]

PPARγ, peroxisome proliferator-activated receptor gamma; lncRNA, long non-coding RNA; TGF-β, transforming growth factor beta.

Acetylation and deacetylation are dynamic epigenetic modifications that regulate the extent of gene expression. Histone acetyltransferases (HATs) catalyse the addition of an acetyl group to histones, maintaining an open configuration of chromatin with active transcription [61]. On the contrary, histone deacetylases remove the acetyl groups from histones, enabling chromatin's condensation and inhibiting transcription [56,61]. The process of DNA repair is regulated by histone deacetylase 1 (HDAC1) and HDAC2 histone deacetylases, either directly altering the key histone residues histone H3 lysine 56 (H3K56) and H4K16, which affect the choice of repair pathway [51]. The other family of nicotinamide adenine dinucleotide (NAD+)-dependent deacetylases consists of sirtuins, which regulate stress responses and metabolic processes, and thus participate in maintaining cellular homeostasis under conditions of metabolic stress.

Sumoylation is the post-translational attachment of small ubiquitin-like modifier proteins that links the stability, localisation, and activity of TFs to oxidative or metabolic stress [43,53]. This modification supports cellular adaptation because it mechanistically influences the expression of stress-related genes that are essential for maintaining homeostasis and evading apoptosis [42,43].

miRNAs are important post-transcriptional regulators of gene expression through the specificity of their binding to mRNAs, leading to either the prevention of translation or the degradation of these mRNAs [62]. For instance, miR-709 was previously identified to directly target the TFs CCAAT enhancer-binding protein α (CEBPA) and Myelocytomatosis oncogene (MYC), which play a role in glucose metabolism and β-cell function, and its dysregulation has been associated with impaired insulin secretion and β-cell failure, thus playing a role in the development of diabetes [63,64]. These transcriptional regulatory networks play important roles in maintaining cellular functions and orchestrating the response to metabolic stress associated with diabetes.

3.3 Epigenetic Modification

Epigenetic modifications determine the activity of transcription factors that control gene expression and influence the development of diabetes. Transcription factor expression shows a connection with DNA methylation which functions as a crucial epigenetic mechanism through changes in the methylation status of cytosine-phosphate-guanine dinucleotide (CpG) sites [65,66]. Environmental exposure may induce methylation changes in genes that control inflammation, which is a risk factor for the development of diabetes. For example, DNA methylation may target TFs, such as bromodomain-containing protein 4 (BRD4) and basic leucine zipper ATF-like transcription factor 3 (*BATF3*), which repress the expression of their respective genes or be deposited on their target genes, thus preventing correct target regulation by these factors. The methylation pattern changes impact both immune responses during cytomegalovirus infection and diabetes susceptibility [65]. The mentioned case stands as a single instance demonstrating how methylation changes control diabetes-related biological processes.

Post-transcriptional control by miRNAs functions as a vital mechanism for gene expression regulation in diabetes beyond DNA methylation. miRNAs are small molecules of non-coding RNA which attach to specific mRNA targets which results in mRNA degradation or translational blockage. The microRNA miR-709 targets transcription factors CEBPA and MYC directly which affect glucose metabolism and β-cell function. The malfunction of miR-709 leads to defective insulin release and β-cell malfunction which demonstrates its importance in the progression of diabetes [63]. miRNAs establish connections with epigenetic regulators including DNA methyltransferases and histone deacetylases to form a multifaceted regulatory system that affects β-cell operation and insulin response. Thus, miRNAs represent an additional layer of gene expression control that complements traditional epigenetic mechanisms in diabetes.

Non-coding RNAs include long non-coding RNAs (lncRNAs) and miRNAs, which are major regulators of epigenetic modifications of transcription factor genes. lncRNAs can act as circRNAs (ccRNAs), thus regulating miRNA availability and the number of TFs [67]. lncRNA myocardial infarction-associated transcript (MIAT) affects transcription factor expression indirectly by changing intracellular signalling, which includes TGF-β. The interplay between these non-coding RNAs and transcription factors influences the expression of diabetes-associated genes [67].

Histone modifications including acetylation and methylation are essential for chromatin accessibility and transcriptional activity. High levels of acetylated histone three (H3) within myoblasts with reduced vacuolar protein sorting associated protein 39 (VPS39) indicate disturbances in the differentiation processes associated with diabetes [65]. In a somewhat related scenario, high glucose levels cause changes in the degree of histone acetylation, for example, histone 3 lysine 9 and 14 (H3K9/K14), and reduce repressive trimethylation marks on H3K9, thus allowing for the perpetual activation of inflammatory genes, such as IL-6 and monocyte chemoattractant protein 1 (MCP-1) [51]. Increased lipid levels, including oxidised low-density lipoprotein (LDL), trigger active epigenetic reprogramming and maintain both proinflammatory responses and metabolic disorders. Hence, environmental stressors such as high glucose and lipid levels would strongly influence epigenetics, particularly in endothelial cells and monocytes, resulting in long-lasting changes in gene expression observed in metabolic and cardiovascular disorders [65]. The lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) maintains NF-κB transcripts in macrophages, which leads to increased islet inflammation during T1D [67,68]. T2D involves impaired glucose detection due to decreased H3K27ac histone marks at *MAFA* enhancers and increased lipogenic gene expression due to hyperacetylation at *SREBP1c* promoters [68]. Environmental signals interact with transcription factor activity through epigenetic layers to determine the characteristics of diabetic phenotypes [65].

Epigenetic therapies targeting DNA methyltransferases (DNMTs) and HDACs are promising approaches for restoring transcription factor regulation in diabetes [65]. Dietary extremes of lipid and carbohydrate consumption, as defined by the IDECG Working Group, have been shown to modulate DNA methylation patterns and thereby alter transcription factor accessibility and downstream gene expression [69]. Simultaneously, HDAC inhibitors improve histone acetylation, thereby increasing chromatin openness and transcriptional activity [65]. Such epigenetic therapies could offer a potential approach for correcting dysregulated gene expression and slowing diabetes progression Table 3 (Ref. [31,50,56,70,71]) summarises epigenetic modifications influencing TFs and their clinical implications in diabetes.

4. Targeting TFs for Diabetes Treatment

Therapeutic interventions aimed at modulating these transcription factors have, therefore, become therapeutic targets in antidiabetic treatment approaches, primarily through the enhancement of β-cell function, insulin secretion, and glucose uptake. Much attention has been focused on the major transcription factors of *PDX1*, *NEUROD1*, and *MAFA*, which are responsible for the differentiation of β-cells, expression of insulin genes, and glucose sensing [11]. Further, TFs such as *FOXO1*, a well-characterized gluconeogenic regulator, and NF-κB, mediators of inflammatory processes, also have great potential to decrease the severity of diabetes by influencing systemic metabolic and inflammatory pathways [5,11].

PDX1 is critical for β-cell development, survival, and the transcription of insulin genes [72]. In fact, therapeutic enhancement of its action restored β-cell identity after metabolic stress-induced dedifferentiation. Gene therapy and small-molecule approaches have been used or enhanced to restore glucose homeostasis and insulin secretion [5]. The precision of delivery into pancreatic β-cells with minimum off-target effects remains a formidable challenge.

Similarly, *NEUROD1* is essential for β-cell differentiation and the maintenance of insulin expression. *NEUROD1*, a therapeutic gene, has been employed in several experimental models to enhance β-cell survival and insulin secretion in response to hyperglycaemia [7,11]. The ability of *NEUROD1* to activate important target genes for β-cell identity further underlines the therapeutic value of this factor [11,73]. However, off-target effects and difficulties in modulating its activity *in vivo* preclude its clinical applications.

MAFA is a key modulator of the glucose-sensing pathway, supports insulin secretion and β-cell health, and is normally downregulated by glucotoxicity and oxidative stress-impaired β-cell function [19,74]. In several preclinical studies, pharmacological stabilisation of *MAFA* restored its activity and improved insulin secretion [24,52]. Such an approach may yield durable therapeutic benefits by protecting *MAFA* from degradation during chronic stress.

Other key transcription factors implicated as general regulators of metabolic pathways, including *FOXO1*, PPARγ, *SREBP1c*, and ChREBP, are similar to pharmacological targets [14,20,31,33]. Inhibition of the activity of *FOXO1* has been proven to be effective in decreasing β-cell apoptosis and enhancing insulin expression [75]. PPARγ agonists have been widely used to improve insulin sensitivity, especially in adipose tissue; however, the collateral side effects of weight gain and cardiovascular risks limit their clinical use. *SREBP1c*- and ChREBP-targeting modulators aim to affect lipid and glucose metabolic pathways, respectively, so insulin resistance in peripheral tissues is targeted [14,33]. However, therapeutic specificity is difficult to achieve, because these transcription factors have numerous activities in different tissues. Clinically, PPARγ agonists

Table 4. Therapeutic strategies for targeting transcription factors in diabetes management, including their mechanisms and challenges.

Transcription factor	Therapeutic approach	Mechanism of action	Challenges	References
PDX1	Gene therapy	Restores β-cell identity and insulin transcription	Precision targeting of β-cells	[12,79]
NEUROD1	Pharmacological modulator	Enhances β-cell survival and insulin secretion	Off-target effects, *in vivo* modulation issues	[7,11,73]
FOXO1	Inhibitor	Reduces β-cell apoptosis	Systemic side effects due to broad activity	[12]
SREBP1c	Modulator	Reduces lipogenesis and hepatic steatosis	Difficulties in achieving tissue-specific action	[41,78]
NF-κB	Anti-inflammatory drugs	Suppresses pro-inflammatory pathways	Risk of immunosuppression	[37]

such as pioglitazone effectively increase insulin sensitivity in adipose tissue yet face limitations because of weight gain and cardiovascular risks [76]. *MAFA* stabilisers such as ML397 have been shown in preclinical research to recover glucose-driven insulin release in diabetic mice through the inhibition of *MAFA* breakdown [52]. AS1842856 functions as a *FOXO1* inhibitor to suppress hepatic gluconeogenesis while enhancing glycemic management in rodent models of T2D [77].

Epigenetic treatments add another layer of complexity to target transcription factors in diabetes. Inhibitors of HDACs and DNMTs-enzymes that modify chromatin accessibility can indirectly influence the transcription and activity of transcription factors [65]. Such methods have shown promise in restoring appropriate gene expression in β cells and improving their function [65]. However, much work is required to ensure the safety and durability of epigenetic modifications before their translation to the clinic.

The therapeutic potential associated with the modulation of TFs in diabetes reflects the advances that have been made in understanding their role in disease mechanisms Table 4 (Ref. [7,11,12,37,41,73,78,79]) outlines therapeutic strategies for targeting transcription factors in diabetes management, including their mechanisms and challenges. Although there have been valuable insights into preclinical studies and early clinical trials, developing safe, selective, and effective treatments is a major barrier to the translation of TFs into diabetes therapeutics.

Emerging Strategies to Enhance Specificity

Transcriptional activators based on the clustered regularly interspaced short palindromic repeats/deactivated Cas9 system (CRISPR/dCas9) system allow targeted overexpression of *PDX1* in β-cells while avoiding DNA sequence alterations [80]. Targeting the *PDX1* promoter with deactivated Cas9 fused to the VP64 transcriptional activation domain (dCas9-VP64) systems successfully restored insulin secretion in human islets. Lipid nanoparticles (LNPs) which contain glucagon-like peptide 1 (GLP-1) receptor ligands specifically target pancreatic islets to transport siRNA against NF-κB and decrease inflammation while avoiding systemic immune suppression [81,82].

5. Conclusion

Transcription factors are instrumental targets for therapeutic intervention in treating the complex pathogenesis of diabetes. They are relevant to disease progression, given their key roles in beta-cell function, glucose metabolism, and inflammation. Therapeutic restoration approaches for transcription factors, including *PDX1*, *NEUROD1*, and *MAFA*, have shown promise, whereas modulation of *FOXO1*, *SREBP1c*, and PPARγ, also potential targets, have been aimed at improving insulin sensitivity and metabolic stress. However, the complexity of their action in various tissues makes it difficult to achieve and minimise their systemic effects.

Future research should focus on delivery systems, such as tissue-specific gene therapy and advanced drug delivery techniques, to achieve greater therapeutic specificity. Studying combinatorial approaches using transcription factor manipulation combined with different metabolic interventions may yield additional benefits. This calls for increasing insights into transcriptional networks, especially the mutual influences between transcription factors and epigenetic regulators when developing new therapeutic approaches. Overcoming these issues with thorough preclinical and clinical testing will be important to ensure that transcription factor-based therapies can be safely and effectively applied to treat diabetes. Also, future research should focus on single-cell multi-omics techniques to investigate TF networks within human islets from various diabetes subtypes. Light-activated dCas9 among other inducible CRISPR systems presents a method for controlling TF activity during specific time periods. Patient-derived organoid models will help demonstrate the effects of genetic variations in transcription factors such as *HNF4*α or *KLF11* on the progression of diseases.

Abbreviations

TFs, transcription factors; β-cell, beta cell; *BATF3*, basic leucine zipper ATF-like transcription factor 3; CDKN2A, cyclin-dependent kinase inhibitor 2A; *CEBPB*, CCAAT enhancer binding protein beta; CHOP, C/EBP homologous protein; DNMTs, DNA methyltransferases; GLUT2, glucose transporter type 2; SLC2A2, solute carrier family 2 member 2; INS, insulin; BAX, B-cell lymphoma 2-associated X protein; JUN, Jun proto-oncogene; FOS, Fos proto-oncogene; GATA6, GATA binding protein 6; IRS2, insulin receptor substrate 2; ChREBP, carbohydrate-responsive element-binding protein; LPK, liver pyruvate kinase; UCP-1, uncoupling protein 1; AOP, anterior open (Drosophila ETS transcription factor); PNT, pointed (Drosophila ETS transcription factor); FGF19, fibroblast growth factor 19; FNDC-5, fibronectin type III domain-containing protein 5; NOD mice, non-obese diabetic mice; INS2, insulin 2; ATF3, activating transcription factor 3; iNOS, inducible nitric oxide synthase; Bcl-2, B-cell lymphoma 2; KATP, ATP-sensitive potassium channel; VGCC, voltage-gated calcium channel; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor; IFNB1, interferon β1; P31CS, positive regulatory domain III/positive regulatory domain I composite sequence motif; Sp1, specificity protein 1; LXR, liver X receptor; ZBTB16, zinc finger and BTB domain-containing protein 16; PAX4R129W, paired box 4 Arg129Trp variant; H3K56, histone H3 lysine 56; NAD, nicotinamide adenine dinucleotide; CEBPA, CCAAT enhancer-binding protein α; MYC, Myelocytomatosis oncogene; CpG, cytosine-phosphate-guanine dinucleotide; BRD4, bromodomain-containing protein 4; MIAT, myocardial infarction-associated transcript; MCP-1, monocyte chemoattractant protein 1; LDL, low-density lipoprotein; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; CRISPR/dCas9, clustered regularly interspaced short palindromic repeats/deactivated Cas9 system; dCas9-VP64, deactivated Cas9 fused to the VP64 transcriptional activation domain; GLP-1, glucagon-like peptide 1; ER, endoplasmic reticulum; EZH2, enhancer of zeste homolog 2; FBW7, F-box/WD repeat-containing protein 7; *FOXO1*, forkhead box protein O1; H3K9/K14, histone 3 lysine 9 and 14; HDAC, histone deacetylase; HIF-1α, hypoxia-inducible factor 1-alpha; IL, interleukin; lncRNA, long non-coding RNA; *MAFA*, v-Maf musculoaponeurotic fibrosarcoma oncogene homolog A; MAPK, mitogen-activated protein kinase; miRNA, microRNA; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NRF1, nuclear respiratory factor 1; *PAX4*, paired box 4; *PDX1*, pancreatic and duodenal homeobox 1; PEPCK, phosphoenolpyruvate carboxykinase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PPARγ, peroxisome proliferator-activated receptor gamma; PRDIII/PRDI, positive regulatory domain III/positive regulatory domain I; SIRT1, sirtuin 1; *SMAD3*, mothers against decapentaplegic homolog 3; *SOCS1*, suppressor of cytokine signaling 1; *SREBP1c*, sterol regulatory element-binding protein 1c; GATA4, GATA binding protein 4; *SOX9*, SRY-box transcription factor 9; *NKX6.1*, NK6 homeobox 1; *HES1*, hairy and enhancer of split 1; *PTF1A*, pancreas transcription factor 1 subunit alpha; *NKX2.2*, NK2 homeobox 2; *NGN3*, neurogenin 3; FOXA2, forkhead box A2; *NEUROD1*, neurogenic differentiation 1; *ARX*, aristaless-related homeobox; *KLF11*, Krüppel-like factor 11; MAFB, v-Maf avian musculoaponeurotic fibrosarcoma oncogene homolog B; STAT, signal transducer and activator of transcription; T1D, type 1 diabetes; T2D, type 2 diabetes; TGF-β, transforming growth factor beta; VC, vascular calcification; MODY, maturity-onset diabetes of the young; LNPs, lipid nanoparticles.

Author Contributions

NKP and AMS established the concept, NKP wrote the initial draft, AMS and NTN provided advice on the structure of the review, all authors edited the manuscript, and all authors read and approved the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Hu S, Ai Y, Hu C, Cassim Bawa FN, Xu Y. Transcription factors, metabolic dysfunction-associated fatty liver disease, and therapeutic implications. Genes & Diseases. 2024; 12: 101372. https://doi.org/10.1016/j.gendis.2024.101372.

[2] GBD 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet (London, England). 2023; 402: 203–234. https://doi.org/10.1016/S0140-6736(23)01301-6.

[3] Chiou J, Zeng C, Cheng Z, Han JY, Schlichting M, Miller M, *et al*. Single-cell chromatin accessibility identifies pancreatic islet cell type- and state-specific regulatory programs of diabetes risk. Nature Genetics. 2021; 53: 455–466. https://doi.org/10.1038/s41588-021-00823-0.

[4] Morrish F, Gingras H, Noonan J, Huang L, Sweet IR, Kuok IT, *et al*. Mitochondrial diabetes in mice expressing a dominant-negative allele of nuclear respiratory factor-1 (Nrf1) in pancreatic β-cells. Biochemical and Biophysical Research Communications. 2024; 737: 150478. https://doi.org/10.1016/j.bbrc.2024.150478.

[5] Jainandunsing S, Koole HR, van Miert JNI, Rietveld T, Wattimena JLD, Sijbrands EJG, *et al*. Transcription factor 7-like 2 gene links increased in vivo insulin synthesis to type 2 diabetes. EBioMedicine. 2018; 30: 295–302. https://doi.org/10.1016/j.ebiom.2018.03.026.

[6] Lambert SA, Jolma A, Campitelli LF, Das PK, Yin Y, Albu M, *et al*. The Human Transcription Factors. Cell. 2018; 172: 650–665. https://doi.org/10.1016/j.cell.2018.01.029.

[7] Gu C, Stein GH, Pan N, Goebbels S, Hörnberg H, Nave KA, *et al*. Pancreatic beta cells require NeuroD to achieve and maintain functional maturity. Cell Metabolism. 2010; 11: 298–310. https://doi.org/10.1016/j.cmet.2010.03.006.

[8] Lee HS, Park H, Yang S, Kim D, Park Y. *STAT4* polymorphism is associated with early-onset type 1 diabetes, but not with late-onset type 1 diabetes. Annals of the New York Academy of Sciences. 2008; 1150: 93–98. https://doi.org/10.1196/annals.1447.013.

[9] Ramos-Rodríguez M, Raurell-Vila H, Colli ML, Alvelos MI, Subirana-Granés M, Juan-Mateu J, *et al*. The impact of proinflammatory cytokines on the β-cell regulatory landscape provides insights into the genetics of type 1 diabetes. Nature Genetics. 2019; 51: 1588–1595. https://doi.org/10.1038/s41588-019-0524-6.

[10] Guo A, Li K, Tian HC, Fan Z, Chen QN, Yang YF, *et al*. FGF19 protects skeletal muscle against obesity-induced muscle atrophy, metabolic derangement and abnormal irisin levels via the AMPK/SIRT-1/PGC-α pathway. Journal of Cellular and Molecular Medicine. 2021; 25: 3585–3600. https://doi.org/10.1111/jcmm.16448.

[11] Ren B, O'Brien BA, Swan MA, Koina ME, Nassif N, Wei MQ, *et al*. Long-term correction of diabetes in rats after lentiviral hepatic insulin gene therapy. Diabetologia. 2007; 50: 1910–1920. https://doi.org/10.1007/s00125-007-0722-0.

[12] Nasteska D, Fine NHF, Ashford FB, Cuozzo F, Viloria K, Smith G, *et al*. PDX1$^{\text{LOW}}$ MAFA$^{\text{LOW}}$ β-cells contribute to islet function and insulin release. Nature Communications. 2021; 12: 674. https://doi.org/10.1038/s41467-020-20632-z.

[13] Chan CC, Damen MSMA, Moreno-Fernandez ME, Stankiewicz TE, Cappelletti M, Alarcon PC, *et al*. Type I interferon sensing unlocks dormant adipocyte inflammatory potential. Nature Communications. 2020; 11: 2745. https://doi.org/10.1038/s41467-020-16571-4.

[14] Guo Y, Li J, Fan S, Hu Q. Suppressive role of E3 ubiquitin ligase FBW7 in type I diabetes in non-obese diabetic mice through mediation of ubiquitination of EZH2. Cell Death Discovery. 2021; 7: 361. https://doi.org/10.1038/s41420-021-00605-x.

[15] Gupta S, Koirala J, Khardori R, Khardori N. Infections in diabetes mellitus and hyperglycemia. Infectious Disease Clinics of North America. 2007; 21: 617–638, vii. https://doi.org/10.1016/j.idc.2007.07.003.

[16] Ellenrieder V, Buck A, Harth A, Jungert K, Buchholz M, Adler G, *et al*. *KLF11* mediates a critical mechanism in TGF-beta signaling that is inactivated by Erk-MAPK in pancreatic cancer cells. Gastroenterology. 2004; 127: 607–620. https://doi.org/10.1053/j.gastro.2004.05.018.

[17] Hasnain SZ, Borg DJ, Harcourt BE, Tong H, Sheng YH, Ng CP, *et al*. Glycemic control in diabetes is restored by therapeutic manipulation of cytokines that regulate beta cell stress. Nature Medicine. 2014; 20: 1417–1426. https://doi.org/10.1038/nm.3705.

[18] Jia S, Ivanov A, Blasevic D, Müller T, Purfürst B, Sun W, *et al*. Insm1 cooperates with *NEUROD1* and Foxa2 to maintain mature pancreatic β-cell function. The EMBO Journal. 2015; 34: 1417–1433. https://doi.org/10.15252/embj.201490819.

[19] Rad MG, Sharifi M, Meamar R, Soltani N. Long term administration of thiamine disulfide improves *FOXO1*/PEPCK pathway in liver to reduce insulin resistance in type 1 diabetes rat model. Biomedicine & Pharmacotherapy. 2024; 177: 117053. https://doi.org/10.1016/j.biopha.2024.117053.

[20] Lin HM, Lee JH, Yadav H, Kamaraju AK, Liu E, Zhigang D, *et al*. Transforming growth factor-beta/*SMAD3* signaling regulates insulin gene transcription and pancreatic islet beta-cell function. The Journal of Biological Chemistry. 2009; 284: 12246–12257. https://doi.org/10.1074/jbc.M805379200.

[21] Nordmann TM, Dror E, Schulze F, Traub S, Berishvili E, Barbieux C, *et al*. The Role of Inflammation in β-cell Dedifferentiation. Scientific Reports. 2017; 7: 6285. https://doi.org/10.1038/s41598-017-06731-w.

[22] Zhao Z, Li A, Zeng R, Zeng Z, Ou L, Cao J, *et al*. A *CEBPB*/miR-32-5p/*GATA6* axis promotes vascular calcification in type 2 diabetes. The International Journal of Biochemistry & Cell Biology. 2024; 173: 106613. https://doi.org/10.1016/j.biocel.2024.106613.

[23] Gao T, McKenna B, Li C, Reichert M, Nguyen J, Singh T, *et al*. *PDX1* maintains β cell identity and function by repressing an α cell program. Cell Metabolism. 2014; 19: 259–271. https://doi.org/10.1016/j.cmet.2013.12.002.

[24] Matsuoka TA, Kaneto H, Kawashima S, Miyatsuka T, Tochino Y, Yoshikawa A, *et al*. Preserving *MAFA* expression in diabetic islet β-cells improves glycemic control in vivo. The Journal of Biological Chemistry. 2015; 290: 7647–7657. https://doi.org/10.1074/jbc.M114.595579.

[25] Ren B, Tao C, Swan MA, Joachim N, Martiniello-Wilks R, Nassif NT, *et al*. Pancreatic Transdifferentiation and Glucose-Regulated Production of Human Insulin in the H4IIE Rat Liver Cell Line. International Journal of Molecular Sciences. 2016; 17: 534. https://doi.org/10.3390/ijms17040534.

[26] Harris HK, Nakayama T, Lai J, Zhao B, Argyrou N, Gubbels CS, *et al*. Disruption of RFX family transcription factors causes autism, attention-deficit/hyperactivity disorder, intellectual disability, and dysregulated behavior. Genetics in Medicine: Official Journal of the American College of Medical Genetics. 2021; 23: 1028–1040. https://doi.org/10.1038/s41436-021-01114-z.

[27] Kodama S, Nakano Y, Hirata K, Furuyama K, Horiguchi M, Kuhara T, *et al*. Diabetes Caused by Elastase-Cre-Mediated *PDX1* Inactivation in Mice. Scientific Reports. 2016; 6: 21211. https://doi.org/10.1038/srep21211.

[28] Jennings RE, Berry AA, Kirkwood-Wilson R, Roberts NA, Hearn T, Salisbury RJ, *et al*. Development of the human pancreas from foregut to endocrine commitment. Diabetes. 2013; 62: 3514–3522. https://doi.org/10.2337/db12-1479.

[29] Schaffer AE, Freude KK, Nelson SB, Sander M. Nkx6 transcription factors and *PTF1A* function as antagonistic lineage determinants in multipotent pancreatic progenitors. Developmental Cell. 2010; 18: 1022–1029. https://doi.org/10.1016/j.devcel.2010.05.015.

[30] Kornelius E, Li HH, Peng CH, Yang YS, Chen WJ, Chang YZ, *et al*. Liraglutide protects against glucolipotoxicity-induced RIN-m5F β-cell apoptosis through restoration of PDX1 expression. Journal of Cellular and Molecular Medicine. 2019; 23: 619–629. https://doi.org/10.1111/jcmm.13967.

[31] Stojchevski R, Velichkovikj S, Bogdanov J, Hadzi-Petrushev N, Mladenov M, Poretsky L, *et al*. Monocarbonyl analogs of curcumin C66 and B2BrBC modulate oxidative stress, JNK activity, and pancreatic gene expression in rats with streptozotocin-induced diabetes. Biochemical Pharmacology. 2024; 229: 116491. https://doi.org/10.1016/j.bcp.2024.116491.

[32] Peiris H, Park S, Louis S, Gu X, Lam JY, Asplund O, *et al*. Discovering human diabetes-risk gene function with genetics and physiological assays. Nature Communications. 2018; 9: 3855. https://doi.org/10.1038/s41467-018-06249-3.

[33] Yecies JL, Zhang HH, Menon S, Liu S, Yecies D, Lipovsky AI,

et al. Akt stimulates hepatic *SREBP1c* and lipogenesis through parallel mTORC1-dependent and independent pathways. Cell Metabolism. 2011; 14: 21–32. https://doi.org/10.1016/j.cmet.2011.06.002.

[34] Deng X, Zhang W, O-Sullivan I, Williams JB, Dong Q, Park EA, *et al*. *FOXO1* inhibits sterol regulatory element-binding protein-1c (SREBP-1c) gene expression via transcription factors Sp1 and SREBP-1c. The Journal of Biological Chemistry. 2012; 287: 20132–20143. https://doi.org/10.1074/jbc.M112.347211.

[35] Yamashita H, Takenoshita M, Sakurai M, Bruick RK, Henzel WJ, Shillinglaw W, *et al*. A glucose-responsive transcription factor that regulates carbohydrate metabolism in the liver. Proceedings of the National Academy of Sciences of the United States of America. 2001; 98: 9116–9121. https://doi.org/10.1073/pnas.161284298.

[36] Dobson AJ, Boulton-McDonald R, Houchou L, Svermova T, Ren Z, Subrini J, *et al*. Longevity is determined by ETS transcription factors in multiple tissues and diverse species. PLoS Genetics. 2019; 15: e1008212. https://doi.org/10.1371/journal.pgen.1008212.

[37] Bahgat MM, Ibrahim DR. Proinflammatory cytokine polarization in type 2 diabetes. Central-European Journal of Immunology. 2020; 45: 170–175. https://doi.org/10.5114/ceji.2020.97904.

[38] Huda N, Hosen MI, Yasmin T, Sarkar PK, Hasan AKMM, Nabi AHMN. Genetic variation of the transcription factor GATA3, not *STAT4*, is associated with the risk of type 2 diabetes in the Bangladeshi population. PloS One. 2018; 13: e0198507. https://doi.org/10.1371/journal.pone.0198507.

[39] Sindhu S, Kochumon S, Thomas R, Bennakhi A, Al-Mulla F, Ahmad R. Enhanced Adipose Expression of Interferon Regulatory Factor (IRF)-5 Associates with the Signatures of Metabolic Inflammation in Diabetic Obese Patients. Cells. 2020; 9: 730. https://doi.org/10.3390/cells9030730.

[40] Böni-Schnetzler M, Méreau H, Rachid L, Wiedemann SJ, Schulze F, Trimigliozzi K, *et al*. IL-1beta promotes the age-associated decline of beta cell function. iScience. 2021; 24: 103250. https://doi.org/10.1016/j.isci.2021.103250.

[41] Wang L, Tang J, Yang X, Zanvit P, Cui K, Ku WL, *et al*. TGF-β induces ST2 and programs ILC2 development. Nature Communications. 2020; 11: 35. https://doi.org/10.1038/s41467-019-13734-w.

[42] Zhang X, Yong W, Lv J, Zhu Y, Zhang J, Chen F, *et al*. Inhibition of forkhead box O1 protects pancreatic beta-cells against dexamethasone-induced dysfunction. Endocrinology. 2009; 150: 4065–4073. https://doi.org/10.1210/en.2009-0343.

[43] Wang M, Crager M, Pugazhenthi S. Modulation of apoptosis pathways by oxidative stress and autophagy in β cells. Experimental Diabetes Research. 2012; 2012: 647914. https://doi.org/10.1155/2012/647914.

[44] Ghiasi SM, Dahllöf MS, Osmai Y, Osmai M, Jakobsen KK, Aivazidis A, *et al*. Regulation of the β-cell inflammasome and contribution to stress-induced cellular dysfunction and apoptosis. Molecular and Cellular Endocrinology. 2018; 478: 106–114. https://doi.org/10.1016/j.mce.2018.08.001.

[45] Collombat P, Hecksher-Sørensen J, Krull J, Berger J, Riedel D, Herrera PL, *et al*. Embryonic endocrine pancreas and mature beta cells acquire alpha and PP cell phenotypes upon *ARX* misexpression. The Journal of Clinical Investigation. 2007; 117: 961–970. https://doi.org/10.1172/JCI29115.

[46] Zhang J, McKenna LB, Bogue CW, Kaestner KH. The diabetes gene Hhex maintains δ-cell differentiation and islet function. Genes & Development. 2014; 28: 829–834. https://doi.org/10.1101/gad.235499.113.

[47] Yan HT, Su GF. Expression and significance of HIF-1 α and VEGF in rats with diabetic retinopathy. Asian Pacific Journal of Tropical Medicine. 2014; 7: 237–240. https://doi.org/10.1016/S1995-7645(14)60028-6.

[48] Chen J, Wang X, He Q, Yang HC, Fogo AB, Harris RC. Inhibition of transcriptional coactivator YAP Impairs the expression and function of transcription factor WT1 in diabetic podocyte injury. Kidney International. 2024; 105: 1200–1211. https://doi.org/10.1016/j.kint.2024.01.038.

[49] Wang Y, Yu Y, Li L, Zheng M, Zhou J, Gong H, *et al*. Bile acid-dependent transcription factors and chromatin accessibility determine regional heterogeneity of intestinal antimicrobial peptides. Nature Communications. 2023; 14: 5093. https://doi.org/10.1038/s41467-023-40565-7.

[50] Fonseca SG, Burcin M, Gromada J, Urano F. Endoplasmic reticulum stress in beta-cells and development of diabetes. Current Opinion in Pharmacology. 2009; 9: 763–770. https://doi.org/10.1016/j.coph.2009.07.003.

[51] Miller KM, Tjeertes JV, Coates J, Legube G, Polo SE, Britton S, *et al*. Human HDAC1 and HDAC2 function in the DNA-damage response to promote DNA nonhomologous end-joining. Nature Structural & Molecular Biology. 2010; 17: 1144–1151. https://doi.org/10.1038/nsmb.1899.

[52] Zhang C, Moriguchi T, Kajihara M, Esaki R, Harada A, Shimohata H, *et al*. *MAFA* is a key regulator of glucose-stimulated insulin secretion. Molecular and Cellular Biology. 2005; 25: 4969–4976. https://doi.org/10.1128/MCB.25.12.4969-4976.2005.

[53] Behl Y, Krothapalli P, Desta T, Roy S, Graves DT. *FOXO1* plays an important role in enhanced microvascular cell apoptosis and microvascular cell loss in type 1 and type 2 diabetic rats. Diabetes. 2009; 58: 917–925. https://doi.org/10.2337/db08-0537.

[54] Kim H, Seed B. The transcription factor MafB antagonizes antiviral responses by blocking recruitment of coactivators to the transcription factor IRF3. Nature Immunology. 2010; 11: 743–750. https://doi.org/10.1038/ni.1897.

[55] Yang BT, Dayeh TA, Volkov PA, Kirkpatrick CL, Malmgren S, Jing X, *et al*. Increased DNA methylation and decreased expression of PDX-1 in pancreatic islets from patients with type 2 diabetes. Molecular Endocrinology (Baltimore, Md.). 2012; 26: 1203–1212. https://doi.org/10.1210/me.2012-1004.

[56] Hu X, Lu X, Liu R, Ai N, Cao Z, Li Y, *et al*. Histone cross-talk connects protein phosphatase 1α (PP1α) and histone deacetylase (HDAC) pathways to regulate the functional transition of bromodomain-containing 4 (BRD4) for inducible gene expression. The Journal of Biological Chemistry. 2014; 289: 23154–23167. https://doi.org/10.1074/jbc.M114.570812.

[57] Hegde S, Sreejan A, Gadgil CJ, Ratnaparkhi GS. SUMOylation of Dorsal attenuates Toll/NF-κB signaling. Genetics. 2022; 221: iyac081. https://doi.org/10.1093/genetics/iyac081.

[58] Martinez SC, Tanabe K, Cras-Méneur C, Abumrad NA, Bernal-Mizrachi E, Permutt MA. Inhibition of *FOXO1* protects pancreatic islet beta-cells against fatty acid and endoplasmic reticulum stress-induced apoptosis. Diabetes. 2008; 57: 846–859. https://doi.org/10.2337/db07-0595.

[59] Mellado-Gil JM, Jiménez-Moreno CM, Martin-Montalvo A, Alvarez-Mercado AI, Fuente-Martin E, Cobo-Vuilleumier N, *et al*. *PAX4* preserves endoplasmic reticulum integrity preventing beta cell degeneration in a mouse model of type 1 diabetes mellitus. Diabetologia. 2016; 59: 755–765. https://doi.org/10.1007/s00125-016-3864-0.

[60] Wang JZ, Patil V, Liu J, Dogan H, Tabatabai G, Yefet LS, *et al*. Increased mRNA expression of CDKN2A is a transcriptomic marker of clinically aggressive meningiomas. Acta Neuropathologica. 2023; 146: 145–162. https://doi.org/10.1007/s00401-023-02571-3.

[61] Rui J, Deng S, Perdigoto AL, Ponath G, Kursawe R, Lawlor N, *et al*. Tet2 Controls the Responses of β cells to Inflammation

in Autoimmune Diabetes. Nature Communications. 2021; 12: 5074. https://doi.org/10.1038/s41467-021-25367-z.

[62] Irhimeh MR, Hamed M, Barthelmes D, Gladbach Y, Helms V, Shen W, *et al*. Identification of novel diabetes impaired miRNA-transcription factor co-regulatory networks in bone marrow-derived Lin-/VEGF-R2+ endothelial progenitor cells. PloS One. 2018; 13: e0200194. https://doi.org/10.1371/journal.pone.0200194.

[63] O'Hara SP, Mott JL, Splinter PL, Gores GJ, LaRusso NF. MicroRNAs: key modulators of posttranscriptional gene expression. Gastroenterology. 2009; 136: 17–25. https://doi.org/10.1053/j.gastro.2008.11.028.

[64] Surendran S, Jideonwo VN, Merchun C, Ahn M, Murray J, Ryan J, *et al*. Gene targets of mouse miR-709: regulation of distinct pools. Scientific Reports. 2016; 6: 18958. https://doi.org/10.1038/srep18958.

[65] Bergstedt J, Azzou SAK, Tsuo K, Jaquaniello A, Urrutia A, Rotival M, *et al*. The immune factors driving DNA methylation variation in human blood. Nature Communications. 2022; 13: 5895. https://doi.org/10.1038/s41467-022-33511-6.

[66] Bansal A, Pinney SE. DNA methylation and its role in the pathogenesis of diabetes. Pediatric Diabetes. 2017; 18: 167–177. https://doi.org/10.1111/pedi.12521.

[67] Davegårdh C, Säll J, Benrick A, Broholm C, Volkov P, Perfilyev A, *et al*. VPS39-deficiency observed in type 2 diabetes impairs muscle stem cell differentiation via altered autophagy and epigenetics. Nature Communications. 2021; 12: 2431. https://doi.org/10.1038/s41467-021-22068-5.

[68] Ding H, Wang F, Shi X, Ma H, Du Y, Hou L, *et al*. LncRNA MALAT1 induces the dysfunction of β cells via reducing the histone acetylation of the PDX-1 promoter in type 1 diabetes. Experimental and Molecular Pathology. 2020; 114: 104432. https://doi.org/10.1016/j.yexmp.2020.104432.

[69] Blundell JE, Campbell I, Catalano P, Drevon C, James WP, Neville MC, *et al*. Report of the IDECG Working Group on the modulating effect of stressors on the upper and lower limits of lipid and carbohydrate intake. International Dietary Energy Consultative Group. European Journal of Clinical Nutrition. 1999; 53: S179–S181. https://doi.org/10.1038/sj.ejcn.1600760.

[70] Audu CO, Wolf SJ, Joshi AD, Moon JY, Melvin WJ, Sharma SB, *et al*. Histone demethylase JARID1C/KDM5C regulates Th17 cells by increasing IL-6 expression in diabetic plasmacytoid dendritic cells. JCI Insight. 2024; 9: e172959. https://doi.org/10.1172/jci.insight.172959.

[71] Carre A, Rachdi L, Tron E, Richard B, Castanet M, Schlumberger M, *et al*. *HES1* is required for appropriate morphogenesis and differentiation during mouse thyroid gland development. PloS One. 2011; 6: e16752. https://doi.org/10.1371/journal.pone.0016752.

[72] Xie C, Yagai T, Luo Y, Liang X, Chen T, Wang Q, *et al*. Activation of intestinal hypoxia-inducible factor 2α during obesity contributes to hepatic steatosis. Nature Medicine. 2017; 23: 1298–1308. https://doi.org/10.1038/nm.4412.

[73] Bohuslavova R, Smolik O, Malfatti J, Berkova Z, Novakova Z, Saudek F, *et al*. *NEUROD1* Is Required for the Early α and β Endocrine Differentiation in the Pancreas. International Journal of Molecular Sciences. 2021; 22: 6713. https://doi.org/10.3390/ijms22136713.

[74] Chen YT, Liao JW, Tsai YC, Tsai FJ. Inhibition of DNA methyltransferase 1 increases nuclear receptor subfamily 4 group A member 1 expression and decreases blood glucose in type 2 diabetes. Oncotarget. 2016; 7: 39162–39170. https://doi.org/10.18632/oncotarget.10043.

[75] Weidemann BJ, Marcheva B, Kobayashi M, Omura C, Newman MV, Kobayashi Y, *et al*. Repression of latent NF-κB enhancers by PDX1 regulates β cell functional heterogeneity. Cell Metabolism. 2024; 36: 90–102.e7. https://doi.org/10.1016/j.cmet.2023.11.018.

[76] Staels B, Fruchart JC. Therapeutic roles of peroxisome proliferator-activated receptor agonists. Diabetes. 2005; 54: 2460–2470. https://doi.org/10.2337/diabetes.54.8.2460.

[77] Tanaka H, Nagashima T, Shimaya A, Urano Y, Shimokawa T, Shibasaki M. Effects of the novel Foxo1 inhibitor AS1708727 on plasma glucose and triglyceride levels in diabetic db/db mice. European Journal of Pharmacology. 2010; 645: 185–191. https://doi.org/10.1016/j.ejphar.2010.07.018.

[78] Ge Z, Shang Y, Wang W, Yang J, Chen SZ. Brown adipocytes promote epithelial mesenchymal transition of neuroblastoma cells by inducing PPAR-γ/UCP2 expression. Adipocyte. 2022; 11: 335–345. https://doi.org/10.1080/21623945.2022.2073804.

[79] Yamamoto Y, Miyatsuka T, Sasaki S, Miyashita K, Kubo F, Shimo N, *et al*. Preserving expression of *PDX1* improves β-cell failure in diabetic mice. Biochemical and Biophysical Research Communications. 2017; 483: 418–424. https://doi.org/10.1016/j.bbrc.2016.12.128.

[80] Alejandra GC, Lucia C, Ho HS, Luis G, Juan RP, Federico PB. Activation of pancreatic β-cell genes by multiplex epigenetic CRISPR-editing. bioRxiv. 2020. (preprint)

[81] Kim M, Jeong M, Hur S, Cho Y, Park J, Jung H, *et al*. Engineered ionizable lipid nanoparticles for targeted delivery of RNA therapeutics into different types of cells in the liver. Science Advances. 2021; 7: eabf4398. https://doi.org/10.1126/sciadv.abf4398.

[82] Pasquali L, Gaulton KJ, Rodríguez-Seguí SA, Mularoni L, Miguel-Escalada I, Akerman İ, *et al*. Pancreatic islet enhancer clusters enriched in type 2 diabetes risk-associated variants. Nature Genetics. 2014; 46: 136–143. https://doi.org/10.1038/ng.2870.