

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository:<https://orca.cardiff.ac.uk/id/eprint/175653/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Wang, Hongyu, Bai, Ran, Wang, Yubing, Qu, Meihua, Zhou, You , Gao, Zhiqin and Wang, Yi 2025. The multifaceted function of FoxO1 in pancreatic  $\beta$ -cell dysfunction and insulin resistance: Therapeutic potential for type 2 diabetes. *Life Sciences* 364 , 123384. 10.1016/j.lfs.2025.123384

Publishers page: <https://doi.org/10.1016/j.lfs.2025.123384>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



# The multifaceted function of FoxO1 in pancreatic $\beta$ -cell dysfunction and insulin resistance: Therapeutic potential for type 2 diabetes

Hongyu Wang<sup>a</sup>, Ran Bai<sup>a</sup>, Yubing Wang<sup>b</sup>, Meihua Qu<sup>b</sup>, You Zhou<sup>c</sup>, Zhiqin Gao<sup>a</sup>, Yi Wang<sup>a,\*</sup>

<sup>a</sup> School of Life Science and Technology, Shandong Second Medical University, Weifang 261021, China

<sup>b</sup> Translational Medical Center, Weifang Second People's Hospital, Weifang 261021, China

<sup>c</sup> Systems Immunity Research Institute, Cardiff University, Cardiff CF14 4XN, UK

## ARTICLE INFO

### Keywords:

FoxO1  
Type 2 diabetes mellitus  
Islet  $\beta$  cell  
Insulin resistance  
AKT

## ABSTRACT

The forkhead box O1 (FoxO1), the first discovered member of the FoxO family, is a critical transcription factor predominantly found in insulin-secreting and insulin-sensitive tissues. In the pancreas of adults, FoxO1 expression is restricted to islet  $\beta$  cells. We determined that in human islet microarray datasets, FoxO1 expression is higher than other FoxO transcription factors. Our analyses of three human islet datasets revealed that FoxO1 expression tends to show a negative correlation with type 2 diabetes and no correlation with body mass index (BMI) between individuals with low levels of HbA<sub>1c</sub> (or ND, non-diabetic) and high levels of HbA<sub>1c</sub> (or T2D, type 2 diabetes). However, FoxO1 function is multifaceted and mainly regulated by post-translational modifications including phosphorylation and deacetylation that involved in pancreatic  $\beta$  cell function and insulin sensitivity. This study summarized the molecular mechanisms underlying the role of FoxO1 activity in pancreatic  $\beta$ -cell dysfunction and insulin resistance in T2D. In addition, we collected the clinical trials of FoxO1 inhibitor and agonist in diabetes, and discussed the therapeutic potential of FoxO1 activity in diabetes treatment.

## 1. Introduction

Recently, it has been reported that approximately 828 million adults globally are afflicted with diabetes. Notably, 59 % of diabetic patients aged 30 and above receive no treatment with oral hypoglycemic drugs or insulin. In most countries, especially low- and middle-income ones, the growth of diabetes treatment lags behind the rising prevalence, resulting in an increasingly heavy burden of diabetes and its untreated manifestations [1]. Type 2 diabetes mellitus (T2D) is primarily characterized by impaired insulin secretion from pancreatic  $\beta$  cells and insulin resistance (IR) in the peripheral tissues, such as liver, adipose tissue and muscle [2]. Insulin secretion in obese diabetic people fails to meet the heightened insulin demand leading to hyperglycemia. Chronic hyperglycemia and hyperlipidemia induce the glycototoxicity and lipotoxicity of pancreatic islets, triggering cytokine and chemokine expression, immune cell infiltration and islet inflammation. This cascade results in  $\beta$  cell apoptosis, dedifferentiation, fibrosis and amyloid deposition, further impairing  $\beta$  cell function and worsening diabetes [3].

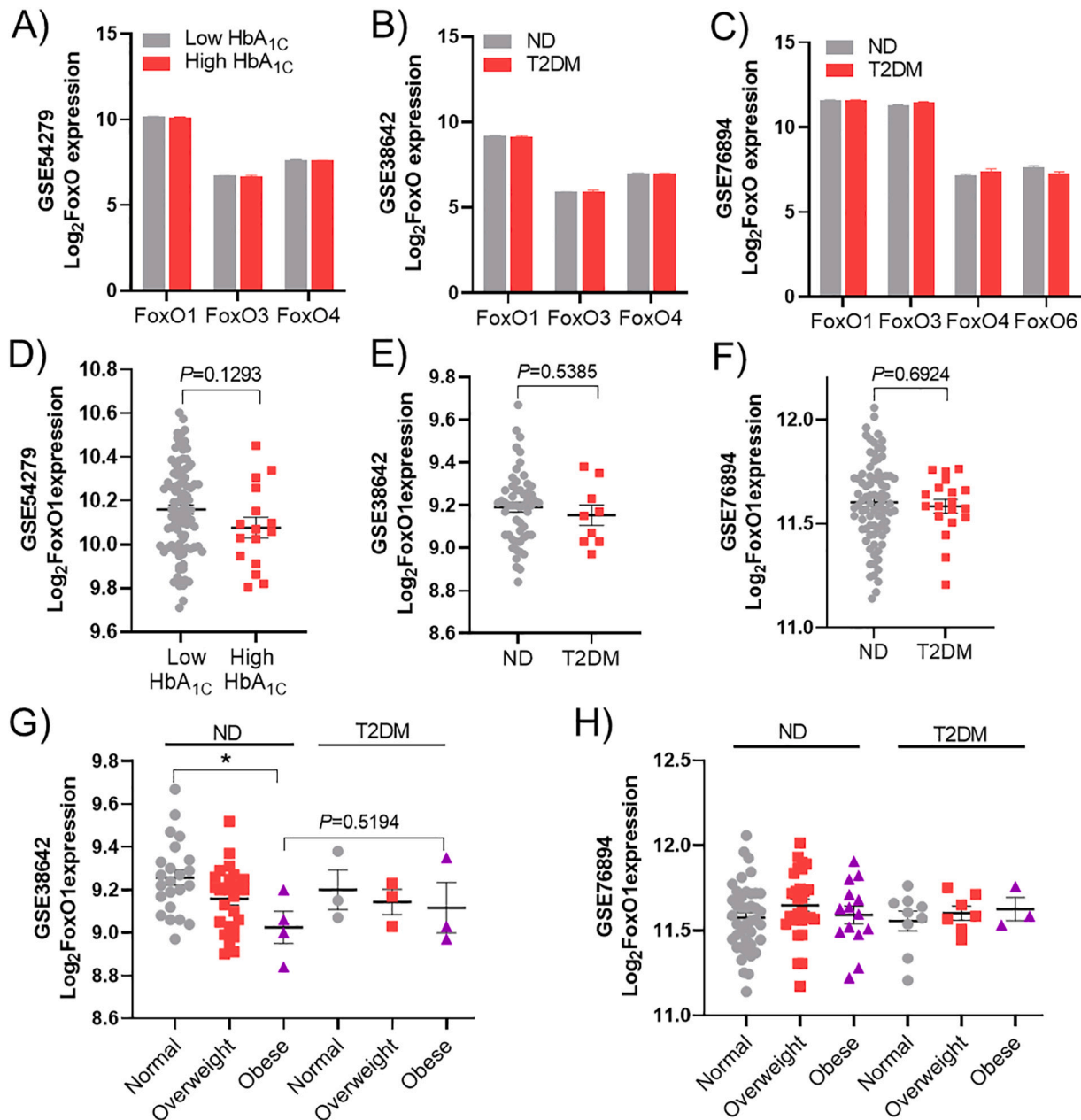
The forkhead box O (FoxO) transcription factors are a key family of transcription factors that regulate target gene expression by binding to specific DNA elements in their promoters in response to internal and

external signals. FoxO proteins are involved in cellular processes such as proliferation, differentiation, metabolism and apoptosis [4]. The FoxO family in mammals comprises four genes: FoxO1, FoxO3a, FoxO4, and FoxO6. Each encodes a distinct forkhead box DNA domain, playing critical roles in regulating the cell cycle, DNA repair, glucose metabolism, apoptosis, autophagy and cellular senescence [5]. Forkhead box O1 (FoxO1) is the earliest identified member of the FoxO family and plays a crucial role as a transcription factor in humans [6]. It is predominantly found in insulin-sensitive and insulin-secreting tissues, including adipocytes, hepatocytes, myocytes, and pancreatic cells. Many studies indicate that FoxO1 influences both insulin synthesis and insulin resistance. In type 2 diabetes, FoxO1 is involved in glucose and lipid metabolism, insulin resistance, and the proliferation, differentiation, and apoptosis of  $\beta$  cells, making it a significant target for potential therapeutic interventions [7]. During human embryonic development, FoxO1 is expressed throughout the pancreas, but in adulthood, its expression is restricted to pancreatic  $\beta$  cells. In healthy individuals, FoxO1 remains inactive in pancreatic  $\beta$  cells but can be activated in response to hyperglycemia. In type 2 diabetes patients, the loss of FoxO1 function in  $\beta$  cells correlates with diminished insulin secretion [8]. Additionally, FoxO1 has been shown to promote adipocyte

\* Corresponding author.

differentiation by regulating insulin, negatively regulate skeletal muscle production, and modulate the expression of type I myofiber genes [9,10]. Prolonged imbalance in FoxO1 activity can lead to the development of hyperglycemia, hyperlipidemia, and hypertension, collectively referred to as the “three highs”, which are fundamental contributors to chronic metabolic diseases [11]. In general, FoxO1 activity is intricately regulated through post-translational modifications, primarily phosphorylation and acetylation, which influence its nuclear translocation and protein stability. Additionally, FoxO1 undergoes ubiquitination-mediated degradation, playing a crucial role in glucose metabolism regulation.

Notwithstanding the profusion of reports on FoxO1, there exists a paucity of comprehensive articles delineating its implications for pancreatic islet function and glycolipid metabolism. In this review, the PubMed database was utilized to search for literatures on FoxO1 published over the past 25 years, spanning from 2001 to 2024. The primary search terms included FoxO1, Insulin,  $\beta$  cell, T2D, Insulin Resistance. Through the individual or combined use of these terms, over 100 articles related to FoxO1 were retrieved, forming the literature foundation for this review. This review explores the effects of FoxO1 on pancreatic  $\beta$  cell function and insulin resistance with the modulating molecular mechanisms. We also summarize the potential application of FoxO1



**Fig. 1.** The expression of FoxO1 in human pancreatic islets. The forkhead box O (FoxO) family of transcription factors expression (Log<sub>2</sub>) in islets of individuals with low (gray) and high (red) HbA<sub>1c</sub> levels, or ND (gray) and T2DM (red) in three datasets. A: GSE54279 ( $n = 113$ ) (<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE54279>); B: GSE38642 ( $n = 63$ ) (<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE38642>); C: GSE76894 ( $n = 103$ ) (<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE76894>); FoxO1 expression (Log<sub>2</sub>) in islets of individuals with low (gray) and high (red) HbA<sub>1c</sub> levels, or ND (gray) and T2DM (red) in the three datasets. D: GSE54279 (Low HbA<sub>1c</sub>:  $n = 94$ , High HbA<sub>1c</sub>:  $n = 19$ ); E: GSE38642 (ND:  $n = 54$ , T2DM:  $n = 9$ ); F: GSE76894 (ND:  $n = 84$ , T2DM:  $n = 19$ ); Islet FoxO1 expression in Normal ( $18.5 \text{ kg/m}^2 \leq \text{BMI} < 25 \text{ kg/m}^2$ , gray), Overweight ( $25 \text{ kg/m}^2 \leq \text{BMI} < 30 \text{ kg/m}^2$ , red), Obese ( $\text{BMI} \geq 30 \text{ kg/m}^2$ , purple) individuals with ND or T2DM in two datasets according to BMI. G: GSE38642 (ND:  $n = 54$ , T2DM:  $n = 9$ ); H: GSE76894 (ND:  $n = 84$ , T2DM:  $n = 19$ ). Statistical test using in the study is *t*-test or Two-way ANOVA (Tukey). Data are presented as mean  $\pm$  SEM. \* $P < 0.05$ . ND, non-diabetic; T2DM, type 2 diabetes mellitus.

inhibitor or agonist in clinical trials. This provides a theoretical foundation for developing and applying FoxO1-targeted therapies in the treatment of T2D.

## 2. The role of FoxO1 in insulin secretion

To examine the impact of FoxO1 expression on type 2 diabetes, we investigated the gene expression data from human pancreatic islets. In the GSE54279 dataset [12], individuals are classified based on blood HbA<sub>1c</sub> levels into low and high HbA<sub>1c</sub> groups. The GSE38642 [13] and GSE76894 [14] datasets classify participants into those with type 2 diabetes mellitus and non-diabetic individuals. Our analysis of FoxO family gene expression in pancreatic islets revealed that FoxO1 expression was highest across the three individual islet sample datasets (Fig. 1A–C). In T2D, the loss of FoxO1 function in islet  $\beta$ -cells is associated with reduced insulin secretion [8]. Guerra et al. [15] reported that glucose-stimulated insulin secretion and insulin mRNA expression in 13 human islet tissue samples from type 2 diabetic patients were lower than in non-diabetic controls, whereas FoxO1 mRNA expression was higher, suggesting that elevated FoxO1 levels may contribute to  $\beta$ -cell dysfunction. Within the three individual islet sample databases, we noted lower FoxO1 expression in the high HbA<sub>1c</sub> group. FoxO1 levels in the diabetic group were slightly lower than those in the non-diabetic group without significant difference (Fig. 1D–F). Moreover, we subdivided the non-diabetic and diabetic groups within GSE38642 and GSE76894 datasets according to the body mass index (BMI) from the World Health Organization criteria. In the GSE38642 dataset, we observed a negative correlation without significance. Conversely, in the GSE76894 dataset, FoxO1 expression in the obese non-diabetic group was higher than in the normal-weight group, while in the diabetic population, a positive correlation was noted, although without significant difference (Fig. 1G–H).

Pancreatic duodenal homeobox-1 (Pdx1) is a crucial transcription factor for pancreatic development and  $\beta$  cell proliferation, differentiation, maturation, and function [16]. Disruption in Pdx1 expression is linked to impaired  $\beta$  cell activity and the pathogenesis of diabetes and other pancreatic disorders. Overexpression of FoxO1 in  $\beta$  cells reduces Pdx1 transcription, leading to defective insulin secretion [17]. In rodent models, FoxO1 pancreatic knock-in (KI) mice exhibit obesity, glucose intolerance, impaired insulin secretion, enlarged islets, and reduced insulin content [18]. However, FoxO1 haploinsufficiency does not alter glucose-stimulated insulin secretion in Insulin receptor substrate 2 (Irs2)<sup>-/-</sup>FoxO1<sup>+/-</sup> mouse islets, nor does the overexpression of wild-type or mutant FoxO1 affect insulin secretion in  $\beta$ TC-3 islet cells [19]. These findings indicated that FoxO1 expression may be associated with insulin secretion. More reports suggest that FoxO1 activity, such as phosphorylation via the phosphatidylinositol 3-kinase (PI3K)/serine/threonine kinase 1 (Akt) signaling pathway, directly influences pancreatic  $\beta$  cell function. In glucose-damaged INS-1 rat pancreatic  $\beta$  cells, increased IRS2 expression and Akt phosphorylation correlate with reduced FoxO1 protein levels and enhanced Pdx1 mRNA expression, resulting in improved glucose-stimulated insulin secretion (GSIS) and intracellular insulin levels [20]. In addition, earlier studies have demonstrated that the islet cell line HIT-T15, when cultured in high concentrations of advanced glycation end products (AGEs), exhibits reduced phosphorylation of FoxO1 and decreased expression and nuclear localization of Pdx1. This results in significantly diminished insulin secretion and content [21]. Beyond phosphorylation by PI3K/Akt, FoxO1 is deacetylated by sirtuins (Sirt1, Sirt3, and Sirt6), NAD<sup>+</sup>-dependent deacetylases primarily located in mitochondria. In db/db mice, intravenous administration of an adenovirus encoding 3 A/LXXAA FoxO1 inhibited the interaction between FoxO1 and Sirt1, reducing the transcriptional activity of FoxO1. This intervention lowered fasting blood glucose levels, improved glucose tolerance, and decreased expression of the G-6-Pase gene, underscoring the critical role of the Sirt1-FoxO1 interaction in regulating glucose metabolism in vivo [22].

Furthermore, histone deacetylases (HDACs) also modulate FoxO1 activity. Specifically, mutations in HDAC4 in mouse pancreatic  $\beta$  cells impair FoxO1 deacetylation, diminish  $\beta$  cell function and insulin secretion, and contribute to the onset of diabetes mellitus [23].

Gupta et al. [24] identified FoxO1 as a key regulator in pancreatic  $\beta$  cells, influencing  $\beta$  cell function through modulation of peroxisome proliferators-activated receptor  $\gamma$  (PPAR $\gamma$ ) and its target genes. Increased FoxO1 activity suppresses the expression of PPAR $\gamma$  and Pdx1, whereas reduced FoxO1 activity enhances their expression, impacting insulin secretion in  $\beta$  cells. Additionally, PPAR $\gamma$  agonists upregulate G protein-coupled receptor GPR40 expression and Akt phosphorylation, while concurrently inhibiting FoxO1 and enhancing Pdx1 expression, thereby promoting insulin secretion in rat insulinoma INS-1 cells [25]. Recent findings suggest that GPR120, another G protein-coupled receptor, may also be a PPAR $\gamma$  target gene, and the combined action of PPAR $\gamma$  and GPR120 enhances insulin sensitivity [26].

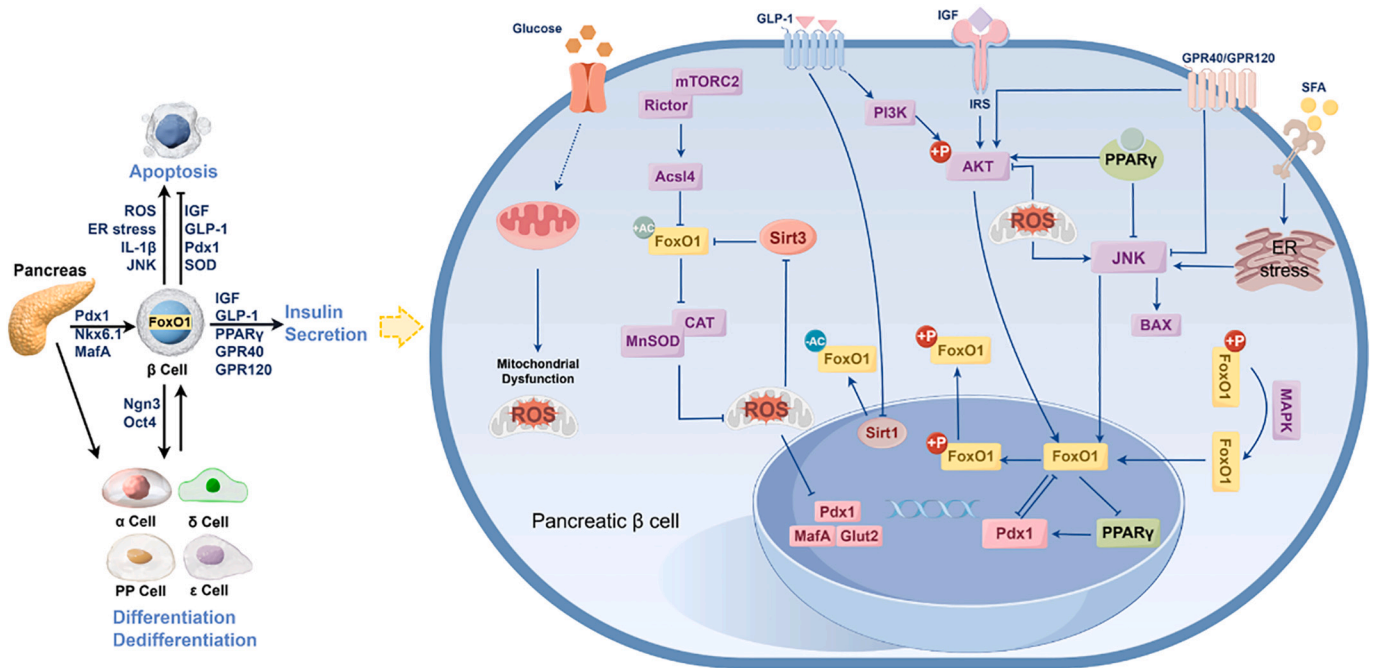
In summary, under normal conditions, the FoxO1 transcription factor is inactive in pancreatic  $\beta$  cells but can be activated by stimuli such as high glucose or lipids, thereby regulating insulin secretion (Fig. 2).

## 3. The role of FoxO1 in oxidative responses of pancreatic $\beta$ cells

Oxidative stress is characterized by oxidative damage resulting from the accumulation of reactive oxygen species (ROS) due to inadequate removal of oxygen free radicals by cells or organisms. ROS play a role in regulating various intracellular signaling pathways, and research indicates that low ROS levels can enhance insulin secretion [27]. However, elevated ROS levels can lead to DNA and protein damage in islets, as well as apoptosis of  $\beta$  cells [28]. Chronic lipotoxicity-induced pancreatic  $\beta$  cell dysfunction is primarily attributed to oxidative stress impairing intracellular signaling pathways [29]. Furthermore, oxidative stress linked to hyperglycemia contributes to abnormal protein accumulation, a recognized mechanism by which hyperglycemia impairs pancreatic  $\beta$  cell function [30]. High glucose levels increase ROS production by activating NADPH oxidase on cell membranes and disrupting the mitochondrial electron transport chain at complex III, thereby compromising antioxidant systems such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) [31].

Oxidative stress resulting from ROS accumulation significantly enhances the transcriptional activity of FoxO1, impacting the expression of antioxidant markers such as SOD and CAT [32]. FoxO1 is known to protect pancreatic  $\beta$  cells from low-level ROS-induced damage by upregulating SOD [33,34]. This protective mechanism involves the deacetylation of FoxO1 by Sirt3 [35]. Sirt3, expressed in pancreatic islets, mitigates ROS production; its reduction is linked to increased ROS levels in high-fat diet-fed rats, whereas Sirt3 overexpression reduces palmitate-induced  $\beta$  cell dysfunction [35,36]. Additionally, Sirt3 deacetylates mitochondrial proteins such as CAT and manganese superoxide dismutase (MnSOD) to alleviate oxidative stress [37]. Zhichen Cai et al. [34] demonstrated that high glucose conditions lead to increased ROS, which downregulates Sirt3. This downregulation enhances FoxO1 acetylation, thereby decreasing the expression of its target proteins MnSOD and CAT [38], thus further elevating ROS levels in db/db mouse islets and high-glucose cultured INS-1  $\beta$  cells. Therefore, Sirt3 may regulate CAT and MnSOD expression via FoxO1, influencing ROS accumulation [34].

Generally, acetylation reduces the transcription level of FoxO1, but under stress, it stabilizes FoxO1, preventing its degradation via ubiquitination. Deacetylation of FoxO1 by sirtuins or HDACs is a strategy to combat oxidative stress. Notably, sirtuins exert a dual regulatory effect on FoxO1, modulating its transcriptional capacity by either retaining it in the cytoplasm or translocating it to the nucleus [39]. Additionally, activation of insulin-like growth factor (IGF-1) has been shown to ameliorate STZ-induced oxidative damage in INS-1 cells through the IRS1/PI3K/Akt/FoxO1 pathway [40]. These findings highlight the Sirt3/FoxO1/SOD/CAT and IGF-1/IRS1/PI3K/Akt/FoxO1 signaling



**Fig. 2.** Molecular mechanisms underlying FoxO1 function in pancreatic  $\beta$  cells. As a fundamental transcription factor, FoxO1 plays an indispensable role in the normal development and differentiation of pancreatic islet cells. In mature islet  $\beta$ -cells, the transcriptional activity of FoxO1 is primarily modulated through phosphorylation, dephosphorylation, acetylation, and deacetylation modifications. On one hand, growth factors such as IGF, GLP-1, or G-protein-coupled receptor (GPR) agonists trigger the activation of the PI3K/Akt signaling cascade. This activation induces the phosphorylation of FoxO1, compelling its export from the nucleus and resulting in a decrease in its transcriptional activity. On the other hand, upon exposure to specific stimuli such as oxidative stress or nutrient deprivation,  $\beta$ -cells respond with the involvement of Sirt family genes, notably Sirt1 and Sirt3, which regulate the deacetylation of FoxO1, promoting its translocation into the nucleus. Once within the nucleus, FoxO1 orchestrates the transcription of downstream target genes, thereby exerting influence over multiple biological processes in pancreatic  $\beta$ -cells, encompassing proliferation, differentiation, apoptosis, and metabolism. FoxO1 directly interacts with specific DNA sequences in the promoter region of the Pdx1 gene, thereby suppressing the transcriptional level of Pdx1. Alternatively, it can indirectly affect the transcription of Pdx1 by regulating other transcription factors such as PPAR $\gamma$ , or signaling pathways like JNK and MAPK. Consequently, these actions lead to a reduction in the expression level of Pdx1 or an impact on its stability, thereby attenuating Pdx1's ability to transcribe target genes including Insulin, MafA and Glut2, and ultimately impacting islet function.

pathways as potential mechanisms underlying  $\beta$  cell damage due to oxidative stress (Fig. 2).

#### 4. The dual role of FoxO1 in proliferation and apoptosis of pancreatic $\beta$ cells

Pancreatic  $\beta$ -cell apoptosis is a primary contributor to islet dysfunction in type 2 diabetes (T2D) patients and rodent models [41]. FoxO1 plays a dual role in regulating  $\beta$ -cell proliferation and apoptosis through multiple signaling pathways and gene expression. Under low-stress conditions, FoxO1 can inhibit apoptosis by activating antioxidant genes like MnSOD, thereby enhancing cellular antioxidant capacity [34]. Conversely, in severe stress conditions, FoxO1 can induce pro-apoptotic genes, promoting apoptosis [42].

In the islets of T2D patients, reduced  $\beta$ -cell mass and increased  $\alpha$ -cell mass are observed, accompanied by downregulated expression of insulin receptor substrates (IRS) and cyclin-dependent kinase 2 (CDK2). Studies with mice lacking insulin receptors specifically in  $\beta$  cells show decreased  $\beta$ -cell mass and increased  $\alpha$ -cell mass. This may result from reduced phosphorylated Akt activity, increased nuclear retention of FoxO1, and decreased CDK2 expression, which together inhibit  $\beta$ -cell proliferation and enhance apoptosis [43]. Saturated free fatty acids and endoplasmic reticulum stress significantly contribute to apoptosis in pancreatic  $\beta$  cells. In studies where MIN6 cells were exposed to high concentrations of palmitate for 4 h, Jun NH (2)-terminal kinase (JNK) activation led to increased nuclear FoxO1. The use of a JNK inhibitor (SP600125) decreased FoxO1 nuclear translocation and activity, thereby reducing  $\beta$ -cell apoptosis [44] (Fig. 2).

Numerous studies have shown that various hormones, growth

factors, and mitokines regulate  $\beta$ -cell proliferation by modulating cell cycle activation and inhibiting apoptosis-related pathways [45,46]. For instance, PI3K can be activated by insulin, insulin-like growth factor 1 (IGF-1), glucagon-like peptide 1 (GLP-1), or glucose-dependent insulinotropic polypeptide (GIP), which then influences downstream Akt. Activated Akt phosphorylates FoxO1 at Ser256 and Thr24, retaining it in the cytoplasm and preventing its binding to nuclear DNA. This process is crucial for balancing  $\beta$ -cell proliferation and apoptosis, thereby supporting pancreatic islet health and function [40,47]. Additionally, ghrelin treatment of MIN6 cells inhibits FoxO1 nuclear translocation and transcriptional activity through the PI3K/Akt pathway, mitigating lipotoxicity-induced apoptosis and functional impairment of pancreatic  $\beta$  cells [48]. Du LJ et al. [49] demonstrated that Banxia Xingxin decoction (BXXD) inhibits apoptosis in MIN6  $\beta$  cells by activating the PI3K/Akt/FoxO1 signaling pathway, offering potential for type 2 diabetes prevention and treatment. Additionally, the Akt/FoxO1 pathway influences  $\beta$ -cell proliferation by modulating Pdx1 activity. The GLP-1 analog liraglutide has been shown to counteract lipotoxicity-induced downregulation of Pdx1, MAF bZIP transcription factor A (MafA), and neuronal differentiation 1 Gene (NeuroD) through PI3K/Akt/FoxO1 modulation, thereby promoting  $\beta$ -cell proliferation [50,51]. Pdx1 expression is regulated by the transcription factor forkhead box A2 (FoxA2), which shares a common DNA binding site on the Pdx1 promoter with FoxO1, leading to competitive binding and inhibition of Pdx1. Studies indicate that Pdx1 and FoxO1 localization in  $\beta$  cells is often mutually exclusive; in Pdx1-positive cells, FoxO1 is typically cytoplasmic, while in other contexts, FoxO1 is primarily located in nuclear [52,53].

In research involving hTERT-MSCs administered to 50 %

pancreatectomized NMRI nude mice via intrapancreatic and intravenous routes, MSCs were found to activate FoxA2 and Pdx1 in pancreatic progenitor cells by downregulating FoxO1 [54]. However, FoxO1 and Pdx1 expression may not be entirely mutually exclusive. Jayron J. et al. [55] reported that knocking down Four and a half LIM domains 2 (FHL2) in MIN6 cells increased Pdx1 mRNA expression even when FoxO1 nuclear localization was enhanced.

In addition to T2D, insulin sensitivity disorders and impaired insulin secretion are also observed in neurodegenerative diseases such as Huntington's, Alzheimer's, and Parkinson's diseases. Research indicates that in Huntington's disease (HD), glucose-stimulated PI3K/Akt/FoxO1 signaling is disrupted in pancreatic  $\beta$  cells. Specifically, IRS-2 expression is reduced and sequestered into mutant huntingtin protein (mHTT) aggregates, preventing glucose-induced PI3K activation. This leads to decreased phosphorylation of Akt and FoxO1, increased apoptosis, and reduced Pdx1 expression in  $\beta$  cells [56]. Beyond phosphorylation, FoxO1 deacetylation significantly influences  $\beta$ -cell proliferation. Studies show that GLP-1 treatment in primary islet and INS cells inhibits Sirt1 activity, decreases Sirt1-FoxO1 binding, and impedes FoxO1 deacetylation, thereby promoting  $\beta$ -cell expansion [57]. In mice with knock-in alleles encoding deacetylated FoxO1, this modification enhances the expression of Ins1/2, Pdx1, MafA, and glucose transporter 2 (GLUT2) in pancreatic islets [58].

FoxO1 plays a crucial role in the proliferation and apoptosis of pancreatic  $\beta$  cells by modulating insulin signaling and the expression of genes essential for islet function. This is closely related to the phosphorylation and acetylation of serine or threonine and lysine residues of FoxO1, processes regulated by multiple signaling pathways, including the INS/IGF-1/Akt and mitogen-activated protein kinase (MAPK) pathways. The INS/IGF-1 signaling pathway activates IRS through binding to the insulin receptor (InR), subsequently activating Akt via PI3K. This cascade results in the phosphorylation and cytoplasmic translocation of FoxO1, thereby diminishing its activation of pro-apoptotic genes and protecting cells from apoptosis [40]. Conversely, MAPK pathway activation can lead to FoxO1 dephosphorylation, enhancing its nuclear activity and promoting apoptosis [59,60] (Fig. 2). Additionally, the microenvironment of  $\beta$  cells including nutrient availability, oxidative stress, and the cell cycle, also influences FoxO1-regulated cell proliferation and apoptosis.

## 5. Effects of FoxO1 on $\beta$ cell differentiation and dedifferentiation

Recent research suggests that  $\beta$  cell dedifferentiation is a significant contributor to  $\beta$  cell loss in diabetic pancreases. Mature pancreatic  $\beta$  cells possess a degree of plasticity, allowing them to dedifferentiate into other cell types lacking insulin secretion, and islet cells can transdifferentiate among themselves [8]. In the progression of type 2 diabetes, pancreatic  $\beta$  cell function may be compromised due to chronic hypersecretion of insulin. This stress can trigger dedifferentiation or transformation of  $\beta$  cells into other cell types, potentially serving as a protective mechanism for  $\beta$  cell function [61].

In both human patients and animal models of type 2 diabetes,  $\beta$  cell dedifferentiation has been observed. This process is marked by the downregulation of  $\beta$  cell-specific transcription factors and upregulation of endocrine progenitor cell markers, inversely correlated with FoxO1 expression [62]. Interestingly, some studies report the absence of FoxO1 in dedifferentiated mouse pancreatic  $\beta$  cells [63]. Targeted knockdown of FoxO1 in mouse  $\beta$  cells does not induce cell death but results in a decrease in  $\beta$  cells, an increase in  $\alpha$  cells, and subsequent hyperglycemia. In studies using cell fate lineage tracking in  $\beta$  FoxO1-specific knockout mice, there is a notable downregulation of key  $\beta$  cell genes such as Pdx1, MafA, and NK6 Homeobox 1 (Nkx6.1). Concurrently, there's an upregulation of markers for endocrine precursor cells, including neurogenin-3 (Ngn3), NeuroD1, and octamer-binding transcription factor 4 (Oct4). This shift from insulin-positive to insulin-negative cells indicates  $\beta$  cell dedifferentiation [61]. Ngn3 is a crucial transcription factor expressed in

pancreatic endocrine progenitor cells during embryogenesis, playing a pivotal role in initiating the differentiation of pancreatic precursor cells into endocrine cells [64].

In experiments involving isolated human fetal pancreatic progenitor cell clusters (18–21 weeks), transfection with FoxO1 siRNA led to a significant increase in Ngn3 and Nkx6.1 expression, thereby negatively impacting pancreatic  $\beta$  cell differentiation [65]. This effect may be associated with the Notch signaling pathway [66]. Conversely, research by Ryotaro Bouchi et al. [67] utilizing intestinal organoids derived from human pluripotent stem cells demonstrated that FoxO1 inhibition fosters the generation of insulin-positive cells. Similarly, Yu et al. [68] used AS1842856, a FoxO1 inhibitor, to promote the differentiation of embryonic stem cells into  $\beta$ -like cells, suggesting a potential strategy for restoring insulin secretion in diabetic patients.

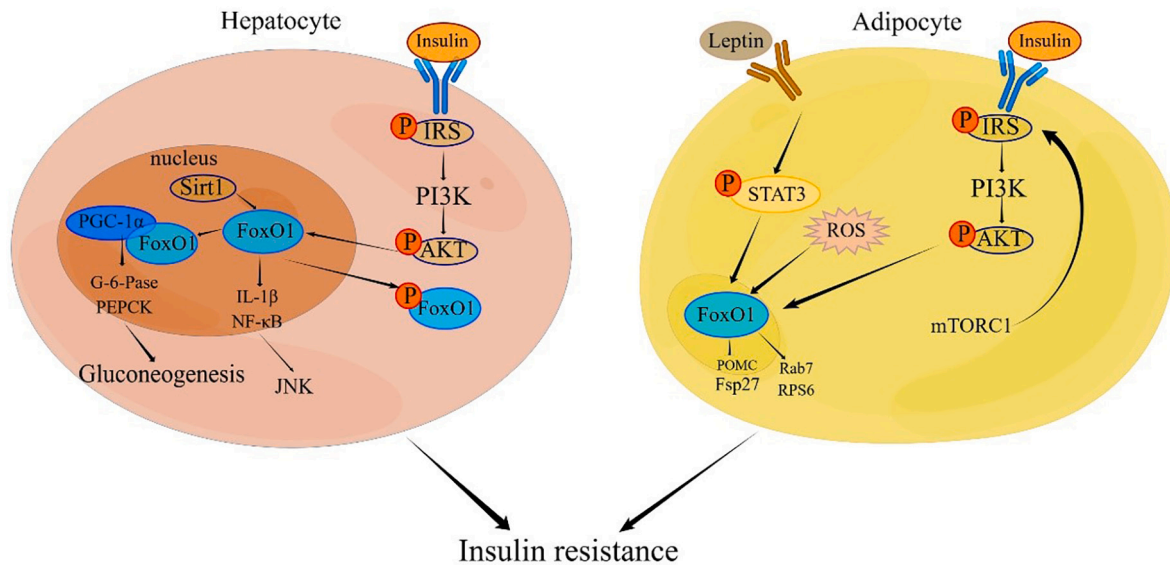
In addition, oxidative stress-induced activation of the JNK pathway in  $\beta$  cells reduces FoxO1 phosphorylation, represses Pdx1 expression, and triggers  $\beta$  cell dedifferentiation and dysfunction [60]. In pancreatic  $\beta$  cells lacking mTOR Complex 2 (mTORC2)/RPTOR independent companion of MTOR complex 2 Gene (Rictor), overexpression of long chain acyl-CoA synthetase 4 (Acsl4) has been linked to increased acetylation and ubiquitination of FoxO1, elevated ROS production, and decreased MafA levels, all contributing to  $\beta$  cell dedifferentiation [69]. Inflammatory cytokines, including Interleukin-1(IL-1), IL-6, and tumor necrosis factor-alpha (TNF- $\alpha$ ), have also been implicated in promoting  $\beta$  cell dedifferentiation. Specifically, IL-1 $\beta$  exposure to human islets downregulates the mRNA expression of FoxO1, MafA, Nkx6.1, and Pdx1 [70]. Furthermore, Kailun Lee et al. [71] reported reduced mRNA levels of Pdx1, Beta2 (NeuroD1), Nkx6.1, and FoxO1 in dedifferentiated  $\beta$  cells from mice with Xbp1 gene deletion.

These studies indicate that FoxO1 plays a multifaceted role in the regulation of pancreatic  $\beta$  cell differentiation and dedifferentiation. FoxO1 influences pancreatic  $\beta$  cell function by modulating the expression of insulin and related genes. Additionally, it is involved in regulating cell stress responses and proliferation, which in turn affects  $\beta$  cell differentiation and survival.

## 6. The role of FoxO1 in insulin resistance

Insulin resistance is a hallmark of type 2 diabetes, characterized by a diminished biological response to insulin in tissues such as the liver and adipose tissue, leading to various metabolic disorders. FoxO proteins are key targets of insulin signaling in the liver and play a crucial role in glucose metabolism regulation [72]. In studies by Garcia Whitlock AE et al. [73], the deletion of FoxO1, 3, and 4 in mouse models resulted in reduced hyperglycemia and prevented hyperinsulinemia, underscoring their involvement in glucose homeostasis.

Typically, postprandial insulin activates the PI3K/Akt signaling pathway, resulting in the phosphorylation and exclusion of FoxO1 from the nucleus. This process inhibits hepatic gluconeogenesis and helps maintain postprandial blood glucose levels within a normal range (Fig. 3). Conversely, during fasting, reduced insulin activity allows FoxO1 to translocate into the nucleus, where it promotes the transcription of glucose-6-phosphatase (G-6-Pase) and phosphoenolpyruvate carboxylase (PEPCK), thereby increasing gluconeogenesis to regulate glycemic balance [74]. In the context of insulin resistance, the expression of these gluconeogenic enzymes is upregulated, leading to increased hepatic gluconeogenesis and glycogenolysis, further exacerbating hyperglycemia [75]. The FoxO1 protein is a key positive regulator of the enzymes PEPCK and G-6-Pase. It promotes their expression by binding to the insulin-responsive element (IRE) in their gene promoters. Research indicates that reduced phosphorylation of FoxO1 enhances its protein levels and transcriptional activity, activating gluconeogenesis-related genes, which in turn increases glucose production and worsens hyperglycemia in insulin-resistant cells [76]. Mice lacking FoxO1 function show inhibited gluconeogenesis, increased insulin sensitivity, and improved fasting glucose levels [77]. Conversely,



**Fig. 3.** The role of FoxO1 in insulin resistance in liver and adipose tissues. A reduction in the responsiveness of insulin-sensitive tissues, including the liver and adipose tissue, to the biological effects of circulating insulin precipitates a cascade of metabolic derangements. In hepatocytes, post-prandial insulin activates the PI3K/Akt signaling pathway, inhibiting hepatic gluconeogenesis and preventing excessive elevation of blood glucose. FoxO1, as a downstream target of Akt, is phosphorylated by p-Akt, leading to its translocation out of the nucleus. Intracellular FoxO1 promotes the expression of PGC-1 $\alpha$ , which regulates the expression of PEPCK and G-6-Pase, consequently, augmenting gluconeogenesis and influencing insulin sensitivity. Additionally, enhanced nuclear localization of FoxO1 induces the expression of inflammatory factors such as NF- $\kappa$ B and IL-1 $\beta$ , and triggers some signaling pathways such as JNK, which further impacts the binding between insulin receptor and insulin receptor substrate (IRS), impeding insulin signal transduction and ultimately contributing to insulin resistance. In adipocytes, FoxO1 would induce leptin resistance by suppressing the Leptin-STAT3-POMC signaling pathway, thereby affecting insulin resistance. ROS generated during fasting are capable of enhancing the transcriptional activity of FoxO1. These events increase the expression of lipid catabolism and antioxidant responses related genes, such as Fsp27 and Rab7. Moreover, the attenuation of the mTORC1-to-IRS feedback is also implicated in insulin resistance under diabetic conditions.

enhanced FoxO1 activity in the liver leads to excessive glucose production, impaired insulin signaling, and upregulation of lipogenesis genes, exacerbating hepatic steatosis and advancing hyperglycemia and hypertriglyceridemia in obese diabetic patients [78]. In db/db mice, high expression and activation of FoxO1 in hepatocytes contribute to glucose intolerance [79]. Inhibition of the interaction between FoxO1 and Sirt1, as well as the transcriptional activity of FoxO1, has been shown to increase liver glycogen content in db/db mice. Conversely, specific knockout of the FoxO1 gene in hepatocytes inhibits gluconeogenesis and mitigates hyperglycemia associated with chronic insulin resistance [80].

FoxO1 is notably overexpressed in individuals with morbid obesity and hyperinsulinemia, promoting the expression of peroxisome proliferator-activated receptor- $\gamma$  coactivator-1 $\alpha$  (PGC-1 $\alpha$ ), thereby enhancing gluconeogenesis and exacerbating obesity-related insulin resistance. Inhibition of FoxO1/PGC-1 $\alpha$  activation has been reported to suppress gluconeogenesis, reduce inflammation, and ameliorate insulin resistance in type 2 diabetes patients [81]. Moreover, FoxO1 regulates several inflammatory mediators implicated in pancreatic resistance. Increased nuclear localization of FoxO1 enhances the expression of inflammatory factors such as NF- $\kappa$ B and IL-1 $\beta$ , and influences signaling pathways including JNK, inhibitor of kappa B kinase (IKK)/NF- $\kappa$ B, protein kinase C (PKC), Suppressor of cytokine signaling (SOCS), and inducible nitric oxide synthase (iNOS)/NO. This leads to abnormal phosphorylation of IRS serine/threonine residues, inhibits IRS tyrosine phosphorylation, reduces the binding affinity of insulin receptors to IRS, impairs insulin signaling, and contributes to insulin resistance [82,83].

In adipose tissue, FoxO1 is highly expressed and localizes to the nucleus, cytoplasm, and mitochondria of adipocytes, responding to various nutrient cues and ROS, such as ROS produced during fasting. This enhances nuclear activity of FoxO1 and initiates the transcription of genes involved in lipid catabolism and antioxidant responses [84]. FoxO1 plays a critical role in lipid metabolism by upregulating autophagy-related proteins, including adipose-specific protein 27

(Fsp27), Ras-related protein Rab7, transcription factor EB (TFEB), and mitochondrial uncoupling proteins [85]. FoxO1-specific inhibitors, such as AS1842856, have been shown to upregulate Fsp27 expression, inhibit autophagy in adipocytes, and reduce adipogenesis [86]. Inhibition of FoxO1 in human adipocytes decreases the expression of key metabolic proteins including the insulin receptor, glucose transporter-4 (Glut4), ribosomal protein S6 (RPS6), RPTOR-independent partner (raptor) of rapamycin target complex (mTOR), and MTOR complex 2. Studies suggest that mTORC1 can regulate the phosphorylation and transcriptional activity of FoxO1. Rajan et al. [87] highlighted that disruption of the mTORC1-to-IRS1 feedback loop may contribute significantly to insulin resistance in diabetes, based on a FoxO1-related insulin signaling model. Additionally, FoxO1 can induce leptin resistance by inhibiting the STAT3-Leptin-Proopiomelanocortin(POMC) signaling pathway, thereby contributing to obesity and insulin resistance [88] (Fig. 3).

As illustrated in Fig. 3 and Table 1, FoxO1 plays a crucial role in maintaining normal insulin signaling. In healthy individuals, inhibition of FoxO1 function may lead to insulin resistance [89]. FoxO1 regulates the expression of antioxidant genes, mitigating oxidative stress often linked with insulin resistance. Additionally, FoxO1 induces autophagy, which is vital for cellular homeostasis and preventing the buildup of damaged proteins and organelles. Thus, comprehending the complex regulatory role of FoxO1 in insulin resistance pathophysiology is essential for developing targeted therapies aimed at enhancing insulin sensitivity and addressing metabolic disorders.

## 7. FoxO1 as a therapeutic target in T2D

The diverse role of FoxO1 in cellular processes and diseases make it an attractive target for drug development. Drugs that inhibit FoxO1 are primarily categorized into small molecule inhibitors and activity modifiers. AS1842856, a small molecule compound, selectively binds to the dephosphorylated, active form of FoxO1. This interaction disrupts the binding of FoxO1 to the IRE consensus site, thereby inhibiting its

**Table 1**  
Overview of the studies related to FoxO1 in insulin resistance.

Mice/tissue/ cell line	FoxO1 function	Effects	Reference
FoxO1-S253A/ A knockin mice	FoxO1 dysfunction	Gluconeogenesis was inhibited, insulin sensitivity was improved and fasting blood glucose was decreased	[77]
T2DM KK-Ay mice db/db mice	FoxO1 inactivation	Increased liver glycogen content	[80]
HepG2 cell	FoxO1 activation	Glucose intolerance	[79]
	FoxO1 enhancement	Abnormal increase in glucose production and impaired insulin action, aggravating liver fat infiltration, promoting hyperglycemia and hypertriglyceridemia in obese diabetics	[78]
High-fat-diet- induced rats	FoxO1/PGC-1 $\alpha$ inhibition	Inhibit gluconeogenesis, reduce inflammation, and reduce insulin resistance in type 2 diabetes patients	[81]
3T3L1 preadipocyte	FoxO1 specific inhibition	Increase the expression of adipose-specific protein 27, inhibit autophagy of adipocytes, reduce adipogenesis and improve lipid metabolism	[86]
Human adipocytes	Decreased FoxO1 activity	IRS, Glut4, RPS6, mTOR and raptor activity were reduced	[87]
HEK293 cell	FoxO1 mutant transfection	Inhibition of the STAT3-Leptin- POMC signaling pathway causes leptin resistance, leading to obesity and insulin resistance	[88]

transcriptional activity and reducing the expression of genes involved in gluconeogenesis [4,90]. In diabetic mice, oral administration of AS1842856 lowers fasting blood glucose levels and enhances glucose tolerance following pyruvate injection, while it has no effect on fasting blood glucose levels in non-diabetic mice [90]. AS1842856, when induced by streptozotocin in diabetic rats, can reduce FoxO1 nuclear translocation in cardiomyocytes, thereby improving cardiac dysfunction, restoring glucose oxidation, alleviating mitochondrial dysfunction, and reducing apoptosis [91]. Additionally, AS1842856 can be applied to insulin-producing cells (IPCs) derived from human embryonic stem cells (hESCs) to enhance the expression of  $\beta$  cell differentiation markers such

as Nkx6.1, Pdx1, insulin, glucokinase (GK), and GLUT2. This treatment promotes the glucose-stimulated insulin secretion (GSIS) response in IPC progeny, offering insights into the use of FoxO1 inhibitors for inducing mature  $\beta$  cells from hESCs [68]. In 2010, Tanaka H et al. [92] identified another small molecule FoxO1 inhibitor, AS1708727, for use in diabetic db/db mice. The study demonstrated that AS1708727 inhibited the expression of G-6-Pase, PEPCK, and gluconeogenesis in the liver of db/db mice, while also reducing apoC-III gene expression. These effects contribute to its antidiabetic and anti-hypertriglyceridemic properties. Additionally, FoxO1 inhibitors have been shown to increase the expression of the cell surface death receptor (FAS) in studies targeting basal-like breast cancer (BBC) and glioblastoma multiforme (GBM) with AS1708727 [93]. Furthermore, Lee YK et al. [94] introduced two oral FoxO1 inhibitors, FBT432 and FBT374, which promote the formation of intestinal  $\beta$ -like cells and enhance glucose tolerance in STZ-induced diabetic mice.

In addition to direct FoxO1 inhibitors, researchers have investigated various compounds targeting components of the FoxO1 signaling pathway. Diazoxide (DZX) has been demonstrated to augment the phosphorylation levels of AKT and FoxO1 by activating mitochondrial potassium channels (mitoKATP), leading to decreased insulin secretion in pancreatic cells [95]. In terms of clinical investigations, current evidence indicates that DZX has been exclusively incorporated into clinical trials related to obesity (Table 2). Metformin has been shown to reduce oxidative stress, enhance autophagy, and alleviate glycolipid disorders through the AMPK/SIRT1-FOXO1 pathway [96]. Insulin sensitizers can modulate FoxO1 activity by improving Akt-mediated phosphorylation of FoxO1 [97]. Additionally, FoxO1 activity can be influenced by activating kinases such as JNK and AMPK [96]. Deletion of miR-223 inhibits Pdx1 and Glut2 expression by reducing Akt phosphorylation and increasing nuclear accumulation of FoxO1, while elevating p27 protein levels, leading to pancreatic dysfunction and insulin resistance [98]. Conversely, miR-223 overexpression suppresses FoxO1 and improves pancreatic cell function, which may be beneficial for diabetes treatment. Recent studies have identified that m6A modifications on FoxO1 mRNA can be demethylated by obesity-associated gene (FTO) proteins, enhancing FoxO1 expression [99]. Supplementation with entacapone, an FTO inhibitor, in diet-induced obese mice reduces body weight and fasting blood glucose levels. Entacapone, on the other hand, has been investigated in clinical trials concerning obesity, schizophrenia, and Parkinson's disease, with the most extensive research being conducted in

**Table 2**  
Overview of the clinical trials of FoxO1 inhibitors and agonists in diabetes (assess at ClinicalTrials.gov).

Product name	Disease	Phase	Study location	Subject	Number of subject	Start date	Completion date	Registry #
DZX	Obesity	II	Netherlands	Adult 25–50 years	51	2008-07	2011-12	NCT00631033
Entacapone	Obesity	I/II	China	Adult 18–60 years	30	2015-01	2015-11	NCT02349243
Resveratrol	Insulin resistance Metabolic syndrome Obesity	NA	United States	Adult 30–60 years	28	2012-10	2018-07	NCT01714102
Resveratrol	T2DM	NA	Netherlands	Adult, older adult 40–70 years	24	2012-05	2014-12	NCT01638780
Resveratrol	Pre-diabetes	NA	Netherlands	Adult, older adult 40–70 years	42	2016-04	2019-03-28	NCT02565979
Resveratrol	Insulin resistance T2DM	II	United States	Adult, older adult 45–65 years	20	2008-03	2017-09-15	NCT01354977
Resveratrol	Obesity Diabetes	II	Singapore	Adult 21–55 years	36	2009-07	2012-10	NCT02247596
Resveratrol	Inflammation Insulin resistance T2DM	III	Italy	Adult, older adult 35–85 years	192	2013-10	2016-02	NCT02244879
Resveratrol	Gestational diabetes	IV	Canada	Adult 18–40 years	112	2014-05	2016-12	NCT01997762
Resveratrol	T2DM	II	Mexico	Adult 30–60 years	22	2016-09	2018-02-01	NCT02549924

NA: not applicable.

the context of Parkinson's disease. In one of the studies on Parkinson's disease (NCT00391898), it was demonstrated that at the conclusion of the study, the efficacy of the combination Levodopa/Carbidopa/Entacapone surpassed that of Levodopa/Carbidopa in Parkinson's disease patients exhibiting early wearing-off symptoms (Table 2).

The application of FoxO1 specific activators remains limited. Resveratrol has been shown to indirectly augment the transcriptional activity and protein abundance of FoxO1, predominantly through the inhibition of the PI3K/Akt signaling cascade and the activation of Sirt1. Li et al. [100] demonstrated that resveratrol, in the context of chronic kidney disease in rats, inhibits tubular injury and glomerulosclerosis by promoting the interaction between FoxO1 and Sirt1, leading to the reduction in the acetylated form of FoxO1. Regarding its clinical trial approvals for diverse diseases, herein, we will solely enumerate those associated with type 2 diabetes mellitus, insulin resistance, and obesity (Table 2). Although substantial progress has been made in the basic research of FoxO1 inhibition and activation, the FoxO1-specific compound is still in its infancy. FoxO1-specific potential therapy is yet to be further explored in clinical T2D treatment.

## 8. Conclusions and prospects

Pancreatic  $\beta$ -cell dysfunction and insulin resistance are hallmark features of type 2 diabetes. This review consolidates current literature on the role of FoxO1 in regulating oxidative stress, proliferation, apoptosis, differentiation, and insulin resistance in pancreatic  $\beta$ -cells, highlighting its involvement in the pathogenesis of type 2 diabetes. FoxO1 serves as a critical transcription factor in pancreatic islet cells, with its activity modulated by various internal and external factors. FoxO1 preserves the normal development of pancreas and participates in glycolipid metabolism via intricate signaling pathways. Typically, FoxO1 maintains  $\beta$ -cell function under low-stress conditions, while its pro-apoptotic effects become more prominent under high-stress scenarios. As a pivotal effector in the INS/IGF-1 signaling pathway and a direct downstream target of PI3K/Akt, FoxO1 transcription is intricately linked to its phosphorylation and acetylation status. The phosphorylation and dephosphorylation of FoxO1 by PI3K/Akt, as well as its acetylation and deacetylation by Sirtuins and mTOR, are key regulatory processes. Additionally, the mTOR pathway and ROS levels influence its transcriptional activity. Inhibition of FoxO1 in type 2 diabetes model animals has been associated with improved gluconeogenesis, glucose tolerance, reduced oxidative stress-induced  $\beta$ -cell damage, and lowered hypertriglyceridemia, while there is no report about FoxO1-specific activator in diabetes management. In summary, FoxO1 plays a multifaceted role in modulating pancreatic  $\beta$ -cell function and insulin sensitivity. The therapeutic potential of FoxO1-targeted compounds needs to be further explored in T2D and other metabolic disorders.

In the prospective research, investigations into FoxO1 are anticipated to commence along three aspects. First, it is imperative to precisely define the molecular mechanisms by which FoxO1 governs downstream gene expression within distinct cell sub-populations. This necessitates an in-depth exploration of the intricate network of interactions between FoxO1 and other transcription factors or signaling cascades. Amidst the complexity of cellular signal transduction, the specific functional nodes of FoxO1, along with its synergistic and antagonistic relationships, need to be accurately identified. For example, a detailed examination of the dynamic binding patterns between FoxO1 and pivotal molecules in the insulin signaling pathway is crucial, as is the analysis of how such binding impacts insulin secretion,  $\beta$ -cell survival or senescence across a spectrum of physiological and pathological states. Second, the focus should be on discerning how the FoxO1 signaling pathway operative in the context of cell metabolism, growth, and differentiation, exerts its influence on glucose, lipid, and amino-acid metabolism. Additionally, the differential effects of FoxO1-mediated metabolic reprogramming on insulin resistance among various diabetes types, including type 1, type 2, and gestational

diabetes, would to be thoroughly investigated. These research undertakings are fundamental for establishing a robust theoretical foundation for personalized therapeutic approaches. Finally, future research endeavors should center on the systematic screening and rational design of small-molecule compounds or biological agents capable of selectively modulating FoxO1 activity. Initiate pre-clinical investigations to stringently assess the efficacy and safety profiles of these agents in a variety of diabetic animal models. Based on the findings, optimize the dosing regimen to achieve the optimal therapeutic outcome. Concurrently, conduct meticulously designed clinical trials to validate the effectiveness and tolerability of FoxO1-targeted treatment strategies in diabetic patients. This holds the potential to introduce novel pharmacotherapeutic options for the management of diabetes.

## CRediT authorship contribution statement

**Hongyu Wang:** Writing – original draft. **Ran Bai:** Writing – original draft. **Yung Wang:** Data curation. **Meihua Qu:** Resources. **You Zhou:** Software, Methodology. **Zhiqin Gao:** Resources, Funding acquisition. **Yi Wang:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Data curation, Conceptualization.

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

All authors reviewed the manuscript and agreed to publish.

## Funding

This study is supported by the National Natural Science Foundation of China (grant no. 82100842; no. 82070856) and the Natural Science Foundation of Shandong Province (grant no. ZR2020QH084; no. ZR201807090175).

## Declaration of competing interest

No potential conflicts of interest relevant to this article were reported.

## Acknowledgements

Not applicable.

## Data availability

The human islet microarray datasets used in the present study are publicly available on <https://www.ncbi.nlm.nih.gov/geo/>. Graphical abstract and Figs. 2 and 3 were originally created by Figdraw (<https://www.figdraw.com>). The clinical trials data was assessed at [ClinicalTrials.gov](https://ClinicalTrials.gov) (<https://ClinicalTrials.gov>).

## References

- [1] NCD Risk Factor Collaboration (NCD-RISC), Worldwide trends in diabetes prevalence and treatment from 1990 to 2022: a pooled analysis of 1108 population-representative studies with 141 million participants, *Lancet* (London, England) 404 (10467) (2024) 2077–2093, [https://doi.org/10.1016/S0140-6736\(24\)02317-1](https://doi.org/10.1016/S0140-6736(24)02317-1).
- [2] H. Mizukami, K. Kudoh, Diversity of pathophysiology in type 2 diabetes shown by islet pathology, *Journal of Diabetes Investigation* 13 (1) (2022) 6–13, <https://doi.org/10.1111/jdi.13679>.
- [3] F. Hu, X. Qiu, S. Bu, Pancreatic islet dysfunction in type 2 diabetes mellitus, *Arch. Physiol. Biochem.* 126 (3) (2020) 235–241, <https://doi.org/10.1080/13813455.2018.1510967>.

- [4] S. Peng, W. Li, N. Hou, et al., A review of FoxO1-regulated metabolic diseases and related drug discoveries, *Cells* 9 (1) (2020) 184, <https://doi.org/10.3390/cells9010184>.
- [5] S. C. S.A. V, D.K. A, FOXO1 mediates vitamin D deficiency-induced insulin resistance in skeletal muscle, *J. Bone Miner. Res.* 31 (3) (2016), <https://doi.org/10.1002/jbmr.2729> (2023-07-09).
- [6] C.G. Kim, H. Lee, N. Gupta, et al., Role of Forkhead Box Class O proteins in cancer progression and metastasis, *Semin. Cancer Biol.* 50 (2018) 142–151, <https://doi.org/10.1016/j.semcancer.2017.07.007>.
- [7] R. Martins, G.J. Lithgow, W. Link, Long live FOXO: unraveling the role of FOXO proteins in aging and longevity, *Aging Cell* 15 (2) (2016) 196–207, <https://doi.org/10.1111/acel.12427>.
- [8] N. Honzawa, K. Fujimoto, The plasticity of pancreatic  $\beta$ -cells, *Metabolites* 11 (4) (2021) 218, <https://doi.org/10.3390/metabol11040218>.
- [9] S. Lee, H.H. Dong, FoxO integration of insulin signaling with glucose and lipid metabolism, *J. Endocrinol.* 233 (2) (2017) R67–R79, <https://doi.org/10.1530/JOE-17-0002>.
- [10] L. García-Prat, E. Perdiguer, S. Alonso-Martín, et al., FoxO maintains a genuine muscle stem-cell quiescent state until geriatric age, *Nat. Cell Biol.* 22 (11) (2020) 1307–1318, <https://doi.org/10.1038/s41556-020-00593-7>.
- [11] M. Bensellam, J.C. Jonas, D.R. Laybutt, Mechanisms of  $\beta$ -cell dedifferentiation in diabetes: recent findings and future research directions, *J. Endocrinol.* 236 (2) (2018) R109–R143, <https://doi.org/10.1530/JOE-17-0516>.
- [12] U. Krus, B.C. King, V. Nagaraj, et al., The complement inhibitor CD59 regulates insulin secretion by modulating exocytotic events, *Cell Metab.* 19 (5) (2014) 883–890, <https://doi.org/10.1016/j.cmet.2014.03.001>.
- [13] J. Taneera, S. Lang, A. Sharma, et al., A systems genetics approach identifies genes and pathways for type 2 diabetes in human islets, *Cell Metab.* 16 (1) (2012) 122–134, <https://doi.org/10.1016/j.cmet.2012.06.006>.
- [14] M. Solimena, A.M. Schulte, L. Marselli, et al., Systems biology of the IMIDIA biobank from organ donors and pancreatocised patients defines a novel transcriptomic signature of islets from individuals with type 2 diabetes, *Diabetologia* 61 (3) (2018) 641–657, <https://doi.org/10.1007/s00125-017-4500-3>.
- [15] S. Del Guerra, R. Lupi, L. Marselli, et al., Functional and molecular defects of pancreatic islets in human type 2 diabetes, *Diabetes* 54 (3) (2005) 727–735, <https://doi.org/10.2337/diabetes.54.3.727>.
- [16] M. Gannon, L.W. Gamer, C.V. Wright, Regulatory regions driving developmental and tissue-specific expression of the essential pancreatic gene *pdx1*, *Dev. Biol.* 238 (1) (2001) 185–201, <https://doi.org/10.1006/dbio.2001.0359>.
- [17] M.Y. Song, J. Wang, S.O. Ka, et al., Insulin secretion impairment in Sirt6 knockout pancreatic  $\beta$  cells is mediated by suppression of the FoxO1-Pdx1-Glut2 pathway, *Sci. Rep.* 6 (2016) 30321, <https://doi.org/10.1038/srep30321>.
- [18] H.J. Kim, M. Kobayashi, T. Sasaki, et al., Overexpression of FoxO1 in the hypothalamus and pancreas causes obesity and glucose intolerance, *Endocrinology* 153 (2) (2012) 659–671, <https://doi.org/10.1210/en.2011-1635>.
- [19] T. Kitamura, J. Nakae, Y. Kitamura, et al., The forkhead transcription factor Foxo1 links insulin signaling to Pdx1 regulation of pancreatic  $\beta$  cell growth, *J. Clin. Invest.* 110 (12) (2002) 1839–1847, <https://doi.org/10.1172/JCI200216857>.
- [20] Y. Liu, S. Mu, W. Chen, et al., Saponins of *Momordica charantia* increase insulin secretion in INS-1 pancreatic  $\beta$ -cells via the PI3K/Akt/FoxO1 signaling pathway, *Endocrinologia, Diabetes Y Nutricion* 68 (5) (2021) 329–337, <https://doi.org/10.1016/j.endien.2021.08.004>.
- [21] A. Puddu, D. Storace, P. Odetti, et al., Advanced glycation end-products affect transcription factors regulating insulin gene expression, *Biochem. Biophys. Res. Commun.* 395 (1) (2010) 122–125, <https://doi.org/10.1016/j.bbrc.2010.03.152>.
- [22] J. Nakae, Y. Cao, H. Daitoku, et al., The LXXLL motif of murine forkhead transcription factor FoxO1 mediates Sirt1-dependent transcriptional activity, *J. Clin. Invest.* 116 (9) (2006) 2473–2483, <https://doi.org/10.1172/JCI25518>.
- [23] M. Gong, Y. Yu, L. Liang, et al., HDAC4 mutations cause diabetes and induce  $\beta$ -cell FoxO1 nuclear exclusion, *Mol. Genet. Genomic Med.* 7 (5) (2019) e602, <https://doi.org/10.1002/mgg3.602>.
- [24] D. Gupta, A.A. Leahy, N. Monga, et al., Peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) and its target genes are downstream effectors of FoxO1 protein in islet  $\beta$ -cells: mechanism of  $\beta$ -cell compensation and failure, *J. Biol. Chem.* 288 (35) (2013) 25440–25449, <https://doi.org/10.1074/jbc.M113.486852>.
- [25] H.S. Kim, Y.C. Hwang, S.H. Koo, et al., PPAR- $\gamma$  activation increases insulin secretion through the up-regulation of the free fatty acid receptor GPR40 in pancreatic  $\beta$ -cells, *PLoS One* 8 (1) (2013) e50128, <https://doi.org/10.1371/journal.pone.0050128>.
- [26] V.A. Paschoal, E. Walenta, S. Talukdar, et al., Positive reinforcing mechanisms between GPR120 and PPAR $\gamma$  modulate insulin sensitivity, *Cell Metab.* 31 (6) (2020) 1173–1188.e5, <https://doi.org/10.1016/j.cmet.2020.04.020>.
- [27] C. Leloup, C. Tourrel-Cuzin, C. Magnan, et al., Mitochondrial reactive oxygen species are obligatory signals for glucose-induced insulin secretion, *Diabetes* 58 (3) (2009) 673–681, <https://doi.org/10.2337/db07-1056>.
- [28] H. Sies, Oxidative stress: a concept in redox biology and medicine, *Redox Biol.* 4 (2015) 180–183, <https://doi.org/10.1016/j.redox.2015.01.002>.
- [29] Y.S. Oh, G.D. Bae, D.J. Baek, et al., Fatty acid-induced lipotoxicity in pancreatic Beta-cells during development of type 2 diabetes, *Front. Endocrinol.* 9 (2018) 384, <https://doi.org/10.3389/fendo.2018.00384>.
- [30] M. Hecker, A.H. Wagner, Role of protein carbonylation in diabetes, *J. Inher. Metab. Dis.* 41 (1) (2018) 29–38, <https://doi.org/10.1007/s10545-017-0104-9>.
- [31] M. Zhu, X. Liu, W. Liu, et al.,  $\beta$  cell aging and age-related diabetes, *Aging* 13 (5) (2021) 7691–7706, <https://doi.org/10.18632/aging.202593>.
- [32] H.S. Tiwari, U.K. Misra, J. Kalita, et al., Oxidative stress and glutamate excitotoxicity contribute to apoptosis in cerebral venous sinus thrombosis, *Neurochem. Int.* 100 (2016) 91–96, <https://doi.org/10.1016/j.neuint.2016.09.003>.
- [33] T. Kitamura, The role of FOXO1 in  $\beta$ -cell failure and type 2 diabetes mellitus, *Nat. Rev. Endocrinol.* 9 (10) (2013) 615–623, <https://doi.org/10.1038/nrendo.2013.157>.
- [34] Z. Cai, S. Liu, Y. Nie, et al., Decreased Sirt3 contributes to cyclic production of reactive oxygen species and islet  $\beta$ -cell apoptosis in high glucose conditions, *Mol. Biol. Rep.* 49 (11) (2022) 10479–10488, <https://doi.org/10.1007/s11033-022-07916-x>.
- [35] M. Kim, J.S. Lee, J.E. Oh, et al., SIRT3 overexpression attenuates palmitate-induced pancreatic  $\beta$ -cell dysfunction, *PLoS One* 10 (4) (2015) e0124744, <https://doi.org/10.1371/journal.pone.0124744>.
- [36] Y. Zhou, A.C.K. Chung, R. Fan, et al., Sirt3 deficiency increased the vulnerability of pancreatic Beta cells to oxidative stress-induced dysfunction, *Antioxid. Redox Signal.* 27 (13) (2017) 962–976, <https://doi.org/10.1089/ars.2016.6859>.
- [37] C.M.O. Volpe, P.H. Villar-Delfino, P.M.F. Dos Anjos, et al., Cellular death, reactive oxygen species (ROS) and diabetic complications, *Cell Death Dis.* 9 (2) (2018) 119, <https://doi.org/10.1038/s41419-017-0135-z>.
- [38] R. Qi, R. Jiang, H. Xiao, et al., Ginsenoside Rg1 protects against d-galactose induced fatty liver disease in a mouse model via FOXO1 transcriptional factor, *Life Sci.* 254 (2020) 117776, <https://doi.org/10.1016/j.lfs.2020.117776>.
- [39] Acetylation of HDAC1 and degradation of SIRT1 form a positive feedback loop to regulate p53 acetylation during heat-shock stress - PubMed[EB/OL]. [2024-07-21]. <https://pubmed.ncbi.nlm.nih.gov/25950477/>.
- [40] F. Cui, X. He, IGF-1 ameliorates streptozotocin-induced pancreatic  $\beta$  cell dysfunction and apoptosis via activating IRS1/PI3K/Akt/FOXO1 pathway, *Inflamm. Res.* 71 (5–6) (2022) 669–680, <https://doi.org/10.1007/s00011-022-01557-3>.
- [41] A.S.M. Moin, A.E. Butler, Alterations in beta cell identity in type 1 and type 2 diabetes, *Curr. Diab. Rep.* 19 (9) (2019) 83, <https://doi.org/10.1007/s11892-019-1194-6>.
- [42] X. Lin, S. Huang, S. Gao, et al., Integrin  $\beta$ 5 subunit regulates hyperglycemia-induced vascular endothelial cell apoptosis through FoxO1-mediated macroautophagy, *Chin. Med. J.* 137 (5) (2024) 565–576, <https://doi.org/10.1097/CM9.00000000000002769>.
- [43] F. Folli, T. Okada, C. Perego, et al., Altered insulin receptor signalling and  $\beta$ -cell cycle dynamics in type 2 diabetes mellitus, *PLoS One* 6 (11) (2011) e28050, <https://doi.org/10.1371/journal.pone.0028050>.
- [44] S.C. Martinez, K. Tanabe, C. Cras-Méneur, et al., Inhibition of Foxo1 protects pancreatic islet beta-cells against fatty acid and endoplasmic reticulum stress-induced apoptosis, *Diabetes* 57 (4) (2008) 846–859, <https://doi.org/10.2337/db07-0595>.
- [45] P. Wang, E. Karakose, H. Liu, et al., Combined inhibition of DYRK1A, SMAD, and Trithorax pathways synergizes to induce robust replication in adult human beta cells, *Cell Metab.* 29 (3) (2019) 638–652.e5, <https://doi.org/10.1016/j.cmet.2018.12.005>.
- [46] J. Charbord, L. Ren, R.B. Sharma, et al., In vivo screen identifies a SIK inhibitor that induces  $\beta$  cell proliferation through a transient UPR, *Nat. Metab.* 3 (5) (2021) 682–700, <https://doi.org/10.1038/s42255-021-00391-x>.
- [47] G. Guan, J. Zhang, S. Liu, et al., Glucagon-like peptide-1 attenuates endoplasmic reticulum stress-induced apoptosis in H9c2 cardiomyocytes during hypoxia/reoxygenation through the GLP-1R/PI3K/Akt pathways, *Naunyn-Schmiedeberg's Arch. Pharmacol.* 392 (6) (2019) 715–722, <https://doi.org/10.1007/s00210-019-01625-2>.
- [48] W. Wang, Y. Liu, Y. Chen, et al., Inhibition of Foxo1 mediates protective effects of ghrelin against lipotoxicity in MIN6 pancreatic beta-cells, *Peptides* 31 (2) (2010) 307–314, <https://doi.org/10.1016/j.peptides.2009.11.011>.
- [49] L.J. Du, B. Pang, Y.M. Tan, et al., Banxia Xiexin decoction ameliorates t-BHP-induced apoptosis in pancreatic beta cells by activating the PI3K/AKT/FOXO1 signaling pathway, *J. Diabetes Res.* 2020 (2020) 3695689, <https://doi.org/10.1155/2020/3695689>.
- [50] S. Shao, M. Nie, C. Chen, et al., Protective action of liraglutide in beta cells under lipotoxic stress via PI3K/Akt/FoxO1 pathway, *J. Cell. Biochem.* 115 (6) (2014) 1166–1175, <https://doi.org/10.1002/jcb.24763>.
- [51] K. Kapodistria, E.P. Tsilibary, E. Kotsopoulou, et al., Liraglutide, a human glucagon-like peptide-1 analogue, stimulates Akt-dependent survival signalling and inhibits pancreatic  $\beta$ -cell apoptosis, *J. Cell. Mol. Med.* 22 (6) (2018) 2970–2980, <https://doi.org/10.1111/jcmm.13259>.
- [52] F. Chen, Y. Zhu, X. Tang, et al., Dynamic regulation of PDX-1 and FoxO1 expression by FoxA2 in dexamethasone-induced pancreatic  $\beta$ -cells dysfunction, *Endocrinology* 152 (5) (2011) 1779–1788, <https://doi.org/10.1210/en.2010-1048>.
- [53] T. Kitamura, J. Nakae, Y. Kitamura, et al., The forkhead transcription factor Foxo1 links insulin signaling to Pdx1 regulation of pancreatic beta cell growth, *J. Clin. Invest.* 110 (12) (2002) 1839–1847, <https://doi.org/10.1172/JCI16857>.
- [54] R. Khatiri, S. Mazurek, S.F. Petry, et al., Mesenchymal stem cells promote pancreatic  $\beta$ -cell regeneration through downregulation of FoxO1 pathway, *Stem Cell Res Ther* 11 (1) (2020) 497, <https://doi.org/10.1186/s13287-020-02007-9>.
- [55] J.J. Habibe, M.P. Clemente-Olivo, T.P.M. Scheithauer, et al., Glucose-mediated insulin secretion is improved in FHL2-deficient mice and elevated FHL2 expression in humans is associated with type 2 diabetes, *Diabetologia* 65 (10) (2022) 1721–1733, <https://doi.org/10.1007/s00125-022-05750-1>.
- [56] L. Li, Y. Sun, Y. Zhang, et al., Mutant huntingtin impairs pancreatic  $\beta$ -cells by recruiting IRS-2 and disturbing the PI3K/AKT/FoxO1 signaling pathway in

- Huntington's disease, *Journal of Molecular Neuroscience*: MN 71 (12) (2021) 2646–2658, <https://doi.org/10.1007/s12031-021-01869-9>.
- [57] P.O. Bastien-Dionne, L. Valenti, N. Kon, et al., Glucagon-like peptide 1 inhibits the sirtuin deacetylase Sirt1 to stimulate pancreatic  $\beta$ -cell mass expansion, *Diabetes* 60 (12) (2011) 3217–3222, <https://doi.org/10.2337/db11-0101>.
- [58] J.Y. Kim-Muller, Y.J.R. Kim, J. Fan, et al., FoxO1 deacetylation decreases fatty acid oxidation in  $\beta$ -cells and sustains insulin secretion in diabetes, *J. Biol. Chem.* 291 (19) (2016) 10162–10172, <https://doi.org/10.1074/jbc.M115.705608>.
- [59] Z. Pan, Z. Tan, H. Li, et al., Diosmetin induces apoptosis and protective autophagy in human gastric cancer HGC-27 cells via the PI3K/Akt/FoxO1 and MAPK/JNK pathways, *Medical Oncology* (Northwood, London, England) 40 (11) (2023) 319, <https://doi.org/10.1007/s12032-023-02180-w>.
- [60] J.J. Ji, L.L. Qian, Y. Zhu, et al., Serpina3c protects against high-fat diet-induced pancreatic dysfunction through the JNK-related pathway, *Cell. Signal.* 75 (2020) 109745, <https://doi.org/10.1016/j.cellsig.2020.109745>.
- [61] C. T. S. X. H.V. L. et al., Pancreatic  $\beta$  cell dedifferentiation as a mechanism of diabetic  $\beta$  cell failure, *Cell* 150 (6) (2012), <https://doi.org/10.1016/j.cell.2012.07.029> (2023-08-06).
- [62] F. Cinti, R. Bouchi, J.Y. Kim-Muller, et al., Evidence of  $\beta$ -cell dedifferentiation in human type 2 diabetes, *J. Clin. Endocrinol. Metab.* 101 (3) (2016) 1044–1054, <https://doi.org/10.1210/clinem.2015-2860>.
- [63] D. Accili, S.C. Talchai, J.Y. Kim-Muller, et al., When  $\beta$ -cells fail: lessons from dedifferentiation, *Diabetes Obes. Metab.* 18 (Suppl. 1) (2016) 117–122, <https://doi.org/10.1111/dom.12723>.
- [64] S. Wang, J.N. Jensen, P.A. Seymour, et al., Sustained Neurog3 expression in hormone-expressing islet cells is required for endocrine maturation and function, *Proc. Natl. Acad. Sci. USA* 106 (24) (2009) 9715–9720, <https://doi.org/10.1073/pnas.0904247106>.
- [65] M. Al-Masri, M. Krishnamurthy, J. Li, et al., Effect of forkhead box O1 (FOXO1) on beta cell development in the human fetal pancreas, *Diabetologia* 53 (4) (2010) 699–711, <https://doi.org/10.1007/s00125-009-1632-0>.
- [66] M. Matsumoto, S. Han, T. Kitamura, et al., Dual role of transcription factor FoxO1 in controlling hepatic insulin sensitivity and lipid metabolism, *J. Clin. Invest.* 116 (9) (2006) 2464–2472, <https://doi.org/10.1172/JCI27047>.
- [67] R. Bouchi, K.S. Foo, H. Hua, et al., FOXO1 inhibition yields functional insulin-producing cells in human gut organoid cultures, *Nat. Commun.* 5 (2014) 4242, <https://doi.org/10.1038/ncomms5242>.
- [68] F. Yu, R. Wei, J. Yang, et al., FoxO1 inhibition promotes differentiation of human embryonic stem cells into insulin producing cells, *Exp. Cell Res.* 362 (1) (2018) 227–234, <https://doi.org/10.1016/j.yexcr.2017.11.022>.
- [69] C. Cui, T. Li, Y. Xie, et al., Enhancing Acs14 in absence of mTORC2/Rictor drove  $\beta$ -cell dedifferentiation via inhibiting FoxO1 and promoting ROS production, *Biochimica Et Biophysica Acta. Molecular Basis of Disease* 1867 (12) (2021) 166261, <https://doi.org/10.1016/j.bbdis.2021.166261>.
- [70] T.M. Nordmann, E. Dror, F. Schulze, et al., The role of inflammation in  $\beta$ -cell dedifferentiation, *Sci. Rep.* 7 (1) (2017) 6285, <https://doi.org/10.1038/s41598-017-06731-w>.
- [71] K. Lee, J.Y. Chan, C. Liang, et al., XBP1 maintains beta cell identity, represses beta-to-alpha cell transdifferentiation and protects against diabetic beta cell failure during metabolic stress in mice, *Diabetologia* 65 (6) (2022) 984–996, <https://doi.org/10.1007/s00125-022-05669-7>.
- [72] W. Guo, D. Li, Y. You, et al., Cystathionine  $\gamma$ -lyase deficiency aggravates obesity-related insulin resistance via FoxO1-dependent hepatic gluconeogenesis, *FASEB J.* 33 (3) (2019) 4212–4224, <https://doi.org/10.1096/fj.201801894R>.
- [73] A.E. Garcia Whitlock, J. Sostre-Colón, M. Gavin, et al., Loss of FOXO transcription factors in the liver mitigates stress-induced hyperglycemia, *Molecular Metabolism* 51 (2021) 101246, <https://doi.org/10.1016/j.molmet.2021.101246>.
- [74] J. Fan, W. Du, J.Y. Kim-Muller, et al., Cyb5r3 links FoxO1-dependent mitochondrial dysfunction with  $\beta$ -cell failure, *Molecular Metabolism* 34 (2020) 97–111, <https://doi.org/10.1016/j.molmet.2019.12.008>.
- [75] J. Altomonte, A. Richter, S. Harbaran, et al., Inhibition of Foxo1 function is associated with improved fasting glycemia in diabetic mice, *Am. J. Physiol. Endocrinol. Metab.* 285 (4) (2003) E718–E728, <https://doi.org/10.1152/ajpendo.00156.2003>.
- [76] K. Benchoula, A. Arya, S. Parhar I, et al., FoxO1 signaling as a therapeutic target for type 2 diabetes and obesity, *Eur. J. Pharmacol.* 891 (2021) 173758, <https://doi.org/10.1016/j.ejphar.2020.173758>.
- [77] K. Zhang, X. Guo, H. Yan, et al., Phosphorylation of forkhead protein FoxO1 at S253 regulates glucose homeostasis in mice, *Endocrinology* 160 (5) (2019) 1333–1347, <https://doi.org/10.1210/en.2018-00853>.
- [78] A. Kamagate, S. Qu, G. Perdomo, et al., FoxO1 mediates insulin-dependent regulation of hepatic VLDL production in mice, *J. Clin. Invest.* 118 (6) (2008) 2347–2364, <https://doi.org/10.1172/JCI32914>.
- [79] An insulin-independent mechanism for transcriptional regulation of Foxo1 in type 2 diabetic mice - PubMed. [2023]. <https://pubmed.ncbi.nlm.nih.gov/34058194/> (07-09).
- [80] L.N. Xu, L.H. Yin, Y. Jin, et al., Effect and possible mechanisms of dioscin on ameliorating metabolic glycolipid metabolic disorder in type-2-diabetes, *Phytomedicine* 67 (2020) 153139, <https://doi.org/10.1016/j.phymed.2019.153139>.
- [81] L. Gu, X. Ding, Y. Wang, et al., Spexin alleviates insulin resistance and inhibits hepatic gluconeogenesis via the FoxO1/PGC-1 $\alpha$  pathway in high-fat-diet-induced rats and insulin resistant cells, *Int. J. Biol. Sci.* 15 (13) (2019) 2815–2829, <https://doi.org/10.7150/ijbs.31781>.
- [82] D. Su, G.M. Coudriet, D. Hyun Kim, et al., FoxO1 links insulin resistance to proinflammatory cytokine IL-1 $\beta$  production in macrophages, *Diabetes* 58 (11) (2009) 2624–2633, <https://doi.org/10.2337/db09-0232>.
- [83] C.J. Teixeira, K. Veras, C.R. De Oliveira Carvalho, Dehydroepiandrosterone on metabolism and the cardiovascular system in the postmenopausal period, *J. Mol. Med. (Berl)* 98 (1) (2020) 39–57, <https://doi.org/10.1007/s00109-019-01842-5>.
- [84] L. Ioannilli, F. Ciccarone, M.R. Ciriolo, Adipose tissue and FoxO1: bridging physiology and mechanisms, *Cells* 9 (4) (2020) 849, <https://doi.org/10.3390/cells9040849>.
- [85] D.W. Sun, Q. Gao, X. Qi, Danshensu ameliorates cardiac Ischaemia reperfusion injury through activating Sirt1/FoxO1/Rab7 signal pathway, *Chin. J. Integr. Med.* 26 (4) (2020) 283–291, <https://doi.org/10.1007/s11655-019-3165-9>.
- [86] L. Liu, L.D. Zheng, P. Zou, et al., FoxO1 antagonist suppresses autophagy and lipid droplet growth in adipocytes, *Cell Cycle* (Georgetown, Tex.) 15 (15) (2016) 2033–2041, <https://doi.org/10.1080/15384101.2016.1192732>.
- [87] M.R. Rajan, E. Nyman, P. Kjølhede, et al., Systems-wide experimental and modeling analysis of insulin signaling through forkhead box protein O1 (FOXO1) in human adipocytes, normally and in type 2 diabetes, *J. Biol. Chem.* 291 (30) (2016) 15806–15819, <https://doi.org/10.1074/jbc.M116.715763>.
- [88] W. Ma, G. Fuentes, X. Shi, et al., FoxO1 negatively regulates leptin-induced POMC transcription through its direct interaction with STAT3, *Biochem. J.* 466 (2) (2015) 291–298, <https://doi.org/10.1042/BJ20141109>.
- [89] M.R. Rajan, E. Nyman, C. Brännmark, et al., Inhibition of FOXO1 transcription factor in primary human adipocytes mimics the insulin-resistant state of type 2 diabetes, *Biochem. J.* 475 (10) (2018) 1807–1820, <https://doi.org/10.1042/BCJ20180144>.
- [90] T. Nagashima, N. Shigematsu, R. Maruki, et al., Discovery of novel forkhead box O1 inhibitors for treating type 2 diabetes: improvement of fasting glycemia in diabetic db/db mice, *Mol. Pharmacol.* 78 (5) (2010) 961–970, <https://doi.org/10.1124/mol.110.065714>.
- [91] D. Yan, Y. Cai, J. Luo, et al., FOXO1 contributes to diabetic cardiomyopathy via inducing imbalanced oxidative metabolism in type 1 diabetes, *J. Cell. Mol. Med.* 24 (14) (2020) 7850–7861, <https://doi.org/10.1111/jcmm.15418>.
- [92] H. Tanaka, T. Nagashima, A. Shimaya, et al., Effects of the novel Foxo1 inhibitor AS1708727 on plasma glucose and triglyceride levels in diabetic db/db mice, *Eur. J. Pharmacol.* 645 (1–3) (2010) 185–191, <https://doi.org/10.1016/j.ejphar.2010.07.018>.
- [93] D. Flores, A. Lopez, S. Udawant, et al., The FOXO1 inhibitor AS1842856 triggers apoptosis in glioblastoma multiforme and basal-like breast cancer cells, *FEBS Open Bio* 13 (2) (2023) 352–362, <https://doi.org/10.1002/2211-5463.13547>.
- [94] Y.K. Lee, W. Du, Y. Nie, et al., Single-agent FOXO1 inhibition normalizes glycemia and induces gut  $\beta$ -like cells in streptozotocin-diabetic mice, *Molecular Metabolism* 66 (2022) 101618, <https://doi.org/10.1016/j.molmet.2022.101618>.
- [95] P. Duan, J. Wang, Y. Li, et al., Opening of mitoKATP improves cardiac function and inhibits apoptosis via the AKT-Foxo1 signaling pathway in diabetic cardiomyopathy, *Int. J. Mol. Med.* 42 (5) (2018) 2709–2719, <https://doi.org/10.3892/ijmm.2018.3832>.
- [96] H. Ren, Y. Shao, C. Wu, et al., Metformin alleviates oxidative stress and enhances autophagy in diabetic kidney disease via AMPK/SIRT1-FoxO1 pathway, *Mol. Cell. Endocrinol.* 500 (2020) 110628, <https://doi.org/10.1016/j.mce.2019.110628>.
- [97] R. Alaaeldin, A.M. Abdel-Rahman I, H.A. Hassan, et al., Carbachromene ameliorates insulin resistance in HepG2 cells via modulating IR/IRS1/PI3k/Akt/GSK3/FoxO1 pathway, *Molecules* (Basel, Switzerland) 26 (24) (2021) 7629, <https://doi.org/10.3390/molecules26247629>.
- [98] Y. Li, S. Deng, J. Peng, et al., MicroRNA-223 is essential for maintaining functional  $\beta$ -cell mass during diabetes through inhibiting both FOXO1 and SOX6 pathways, *J. Biol. Chem.* 294 (27) (2019) 10438–10448, <https://doi.org/10.1074/jbc.RA119.007755>.
- [99] Identification of entacapone as a chemical inhibitor of FTO mediating metabolic regulation through FOXO1, PubMed, 2024. <https://pubmed.ncbi.nlm.nih.gov/30996080/> (08-12).
- [100] P. Li, X. Song, D. Zhang, et al., Resveratrol improves left ventricular remodeling in chronic kidney disease via Sirt1-mediated regulation of FoxO1 activity and MnSOD expression, *BioFactors* (Oxford, England) 46 (1) (2020) 168–179, <https://doi.org/10.1002/biof.1584>.