Role of transcription factor FOXM1 in diabetes and its complications (Review)

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Abstract. Diabetes mellitus is a chronic metabolic disease commonly associated with complications such as cardiovascular disease, nephropathy and neuropathy, the incidence of which is increasing yearly. Transcription factor forkhead box M1 (FOXM1) serves an important role in development of diabetes and its complications. The present study aimed to review the association between FOXM1 with pathogenesis of diabetes and its complications. FOXM1 may be involved in development and progression of diabetes and its complications by regulating cell biological processes such as cell cycle, DNA damage repair, cell differentiation and epithelial-mesenchymal transition. FOXM1 is involved in regulation of insulin secretion and insulin resistance, and FOXM1 affects insulin secretion by regulating expression of insulin-related genes and signaling pathways; FOXM1 is involved in the inflammatory response in diabetes, and FOXM1 can regulate key genes associated with inflammatory response and immune cells, which in turn affects occurrence and development of the inflammatory response; finally, FOXM1 is involved in the regulation of diabetic complications such as cardiovascular disease, nephropathy and neuropathy. In summary, the transcription factor FOXM1 serves an important role in development of diabetes and its complications. Future studies should explore the mechanism of FOXM1 in diabetes and find new targets of FOXM1 as a potential treatment for diabetes and its complications.

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Contents

1. Introduction

Diabetes mellitus (DM) is a common metabolic disease, and the number of people aged 20-79 with diabetes is expected to increase to 642 million by 2040 (1). Patients with diabetes often exhibit complications, such as cardiovascular disease, neuropathy and retinopathy, which have impact patient life and health (2,3). Therefore, it is important to study the pathogenesis and treatment of diabetes and its complications (4-6). The transcription factor forkhead box M1 (FOXM1) is widely present in a variety of cells and serves an important regulatory role in biological processes such as cell cycle, DNA damage repair and cell differentiation (7,8). FOXM1 also serves an important role in development of diabetes and its complications (9-31). FOXM1 is involved in regulating the cell cycle, promoting cell proliferation, maintaining normal cellular differentiation and DNA damage repair (11,12,32). In addition, FOXM1 may be involved in regulating onset and progression of diabetic complications, such as cardiovascular disease and nephropathy (13,33). The present study aimed to review the role of FOXM1 in diabetic complications in terms of its expression, regulatory mechanism and function, and provide new ideas and approaches for the prevention and treatment of diabetes. Studies have shown that FOXM1 is abnormally expressed in diabetic patients, especially in patients with diabetic foot ulcer (DFU) (9,10,15,31), cardiovascular disease (11,12), diabetic nephropathy (DN) (14), neuropathy (25,26) and erectile dysfunction (Fig. 1) (30). The aforementioned studies suggest that FOXM1 may be involved in regulation of the development of diabetes and its complications. Studies have shown that multiple signaling

pathways and molecules regulate the expression and activity of FOXM1, such as YAP1/Akt/glycogen synthase kinase-3 (GSK3β)/FOXM1 (11), VEGF/FOXM1 (30), pituitary adenylate cyclase-activating polypeptide (PACAP)/FOXM1 (25,34), vasoactive intestinal polypeptide (VIP)/FOXM1 (25,35), IL-6/STAT3/FOXM1 (26,27), PI3K/Akt/FOXM1 (36), Ras-ERK/FOXM1 and JNK/p38MAPK/FOXM1 (7). Therefore, FOXM1 may be a key node in the regulation of these signaling pathways and molecules in diabetes and its complications. FOXM1 can regulate the expression of various genes, such as the cell cycle regulatory genes polo-like Kinase 1 (PLK1) and Centromere protein A (CENP-A) (18,29), DNA damage repair genes (Aurora kinase B, Baculoviral IAP Repeat-Containing Protein 5, BUB1 mitotic checkpoint serine/threonine kinase B, centromere protein E, Signal STAT3) (9) and apoptosis-associated genes growth Arrest-specific Transcripts (GAS5), TATA-Box Binding Protein Associated Factor 15 (TAF15) and stromal cell derived factor 4 (SDF4) (31). In addition, some studies have found that FOXM1 may also regulate DM and its complications through the function of immune cells (including T and B cells, monocytes, macrophages, and dendritic cells) (9,10,37). Thus, FOXM1 may be involved in development of diabetes and its complications by regulating the expression of these genes.

In the present study, PubMed database was searched for 'FOXM1 and diabetes mellitus and its complications' between 2000 and 2023 (pubmed.ncbi.nlm.nih.gov/?term=FOXM1+and+diabetes+mellitus+and+its+complications&filter=dates.2000%2F1%2F1-2023). Results were mainly published in the past five years. The present study reviews the role and function of FOXM1 in diabetes and its complications through gene expression and gene regulation. It was hypothesized that FOXM1 is involved in regulating insulin (INS) secretion and resistance, the inflammatory response and development and progression of complications in diabetes. Studies have confirmed that FOXM1 is a key regulator of the development of diabetes and its complications (9-31).

2. FOXM1 in regulation of INS secretion and resistance

FOXM1 is a transcription factor, in islet cells FOXM1 is involved in the regulation of INS secretion (38,39) (Fig. 2). Studies have shown that in islet cells, FOXM1 regulates the expression of INS secretion-related genes, or is regulated to promote INS synthesis and secretion, including INS, type 1 glucose transporter (GLUT1), GLUT2, INS-like growth factor-I (IGF-I), leptin and adiponectin (38-40). Saavedra-García *et al* (41) confirmed that the FOXO3-FOXM1 axis regulates fatty acid metabolism. Studies have shown that glucokinase-mediated glucose metabolism promotes adaptive β-cell proliferation-induced INS synthesis and secretion via activation of the FOXM1/PLK1/CENP-Apathway(18,25,29,36,37).Acetylcholine, PACAP and VIP promote adaptive β-cell proliferation via upregulation of FOXM1 (25,42,43). STAT3/FOXM1/GLUT1 pathway signaling regulates aerobic glycolysis and upregulation of GLUT expression promotes glucose-stimulated INS secretion in human and mouse β-cells (44,45). Glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors potentially compensate for dysregulated β-cell glucose metabolism (18).

In addition, FOXM1 is involved in regulation of INS resistance (IR). The causes of IR in obesity and type 2 DM (T2DM) are not limited to impaired INS signaling but also involve complex interactions of multiple metabolic pathways. Metabolites are regulated by modulating components of INS signaling pathways such as JAK2/STAT3, IKK/NF-κB, JNK/p38MAPK and PI3K/AKT signaling pathways (46-50). Zarrouki *et al* (51) found that plasma FOXM1 levels are increased and positively correlated with IR. FOXM1 mediates multiple IR-associated JAK2/STAT3, NF-κB and PI3K/Akt pathways. FOXM1 expression could be regulated through the JAK2/STAT3 pathway (52); upregulation of FOXM1 increases NF-κB expression (53). FOXO3 and FOXM1 forkhead box transcription factors downstream of PI3K/Akt and JNK/p38MAPK signaling cascades act downstream of PI3K/Akt and JNK/p38MAPK signaling cascades and are key for cell proliferation, differentiation, cell survival, senescence, DNA damage repair and cell cycle control (7).

FOXM1 can also influence the development and progression of IR through pathways such as regulation of fatty acid metabolism and inflammatory responses. Elevated free fatty acid (FFA)-induced lipotoxicity may play an important role in the pathogenesis of β-cell IR (33,54,55). Mangiferin improves IR in HepG2 and C2C12 cells by increasing glucose consumption and promoting serum FFA oxidation via the PPARα pathway (56). Oxidative phosphorylation (OXPHOS) is linked to increased levels of reactive oxygen species (ROS), which are key signaling molecules; production of excess ROS can have deleterious effects, ultimately leading to cell death. By linking FOXM1-dependent peroxiredoxin-3 (Prx3) expression and fatty acid oxidation-mediated NADPH regeneration, Cancer stem cells (CSCs) with increased levels of OXPHOS maintain low ROS levels. FOXM1-dependent ROS regulation is an intracellular resistance mechanism in cancer dry-like cells (57). Nutritional overload triggers an uncontrolled inflammatory response, leading to chronic low-grade inflammation that promotes IR (58). In particular, overexpression of FOXM1 inhibits the inflammatory response following myocardial infarction, thereby protecting the heart. Conversely, inhibition of FOXM1 activity abolishes the cardioprotective effect (59).

Taken together, FOXM1 serves an important role in the regulation of INS secretion and resistance and may be a potential target for the treatment of diabetes.

3. FOXM1 in the inflammatory response in diabetes

FOXM1 is involved in regulating the inflammatory response associated with diabetes. FOXM1 is involved in pathogenesis of diabetes by regulating the expression of inflammation-associated mediators (IL-1, IL-6, TNF-α) and cellular chemokines (monocyte Chemoattractant Protein-1, C-X3-C motif chemokine ligand 1) are expressed and involved in the pathogenesis of diabetes (60-63). In addition, FOXM1 also regulates certain inflammation-associated signaling pathways, such as Wnt/β-catenin (64), JAK/STAT (65), NF-κB (66), SMAD3 (67) and P38MAPK (7) (Fig. 3). FOXM1 deubiquitination could be induced through the Wnt/β-catenin signaling pathway, stabilizing the structure and expression of FOXM1, thereby transporting β-catenin into the nucleus and promoting the transcription of genes related to the biological behavior

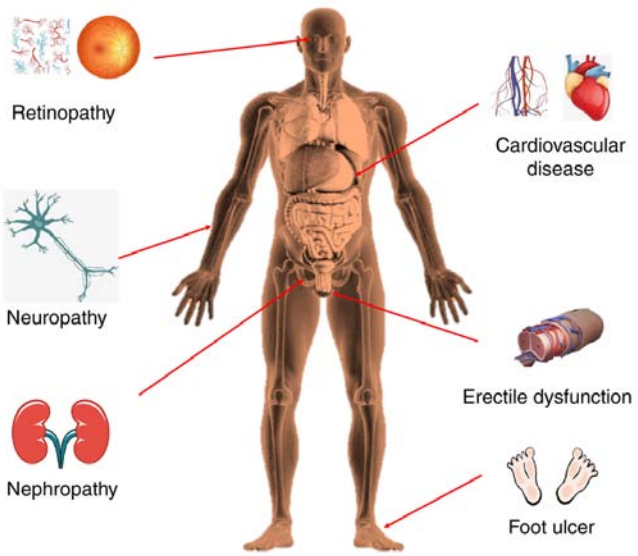

Figure 1. Diabetic complications. Diabetes develops a variety of complications, including nephropathy, diabetic retinopathy, diabetic cardiovascular disease, diabetic erectile dysfunction, diabetic foot ulcers, and diabetic neuropathy.

of inflammation (68). FOXM1 activates the Wnt/β-catenin via transcriptional regulation of multiple Wnt expression signaling pathways and promotes renal fibrosis (64). Silencing of FOXM1 prevents the effects of apoptosis, inflammation, NF-κB and JAK/STAT signaling pathway activation. Moreover, the expression of FOXM1 is positively correlated with the expression of p38MAPK and NF-κB and induces expression of inflammatory factors and amplification of the inflammatory response cascade via the p38MAPK/NF-κB signaling pathway (65). It has been proposed that FOXM1 can directly interact with Smad3 protein to promote Smad3 nuclear retention and bind to β-catenin promoter sequence to promote fibrosis (69). microRNA-4429 targeting FOXM1 can decrease expression of SMAD3 and impede cell proliferation, migration, invasion and epithelial-mesenchymal transition. High expression of FOXM1 increases secretion of T helper and 2 cytokines and promotes inflammatory responses mediated by PI3K/AKT/GSK-33 and p38MAPK signaling pathways. These findings suggest that FOXM1 serves an important regulatory role in the inflammatory response. Therefore, FOXM1 may be a potential target for diabetes therapy.

In DFUs, major transcriptional networks lead to decreased neutrophil and macrophage recruitment and a poorly controlled inflammatory response. The functions of transcription factors FOXM1 and STAT3 are required to activate and promote survival of immune cells, yet expression of transcription factors FOXM1 and STAT3 are suppressed in DFUs. Furthermore, inhibition of FOXM1 (streptozotocin-induced and Leprdb mutant mice-db/db) in a diabetic mouse model results in delayed diabetic wound healing and reduced neutrophil and macrophage recruitment *in vivo*. This shows that a disordered and ineffective inflammatory response is a key factor in the pathogenesis of DFUs, which is facilitated by FOXM1-mediated relaxation of neutrophil and macrophage recruitment, revealing a potential therapeutic strategy (9).

FOXM1 modulates the function of immune cells in diabetic patients, thereby influencing the extent and duration of the inflammatory response (9,37). Thus, FOXM1 may be a potential target for the treatment of diabetes and associated immune diseases. Future studies should explore the mechanism of FOXM1 action in immune cells in diabetic patients and develop FOXM1 inhibitors as novel drugs for the treatment of diabetes and associated immune diseases.

4. FOXM1 in regulating the development and progression of diabetic complications

FOXM1 serves an important role in the complications of DM. Persistent hyperglycemia, hyperinsulinemia and subsequent oxidative stress lead to diabetic complications, primarily classified as microvascular (nephropathy, retinopathy and neuropathy) and macrovascular (cardiomyopathy) complications (70). Studies have shown that FOXM1 is abnormally expressed in diabetic patients with nephropathy, retinopathy, cardiovascular disease, DFU and tumors (9-12,14,71). FOXM1 is involved in the development and progression of complications of diabetes via multiple pathways, including regulation of cell proliferation, apoptosis, inflammatory response, oxidative stress and angiogenesis. In DN renal tissue, FOXM1 is lowly expressed. FOXM1 overexpression improves renal function in mice, decreases pathological changes and increases the expression of the podocyte marker nephrin in renal tissue (14). In diabetic retinopathy (DR), FOXO1 is aberrantly expressed and the FOXM1/FOXO1 axis is involved in regulating development and progression of DR (72,73). In diabetic cardiovascular complications, FOXM1 is overexpressed in myocardial tissue in a hyperglycemic state, leading to increased cardiomyocyte hypertrophy and fibrotic response (11). Maternally imprinted gene (MEG3) promotes degradation of FOXM1 protein by promoting FOXM1 ubiquitination, thereby decreasing VEGF expression and ultimately regulating endothelial differentiation of bone marrow mesenchymal stem cells (BM-MSCs). MEG3/FOXM1 controls differentiation of BM-MSCs to endothelial cells (ECs) (30). FOXM1 regulates ROS levels in neutrophils and inhibition of FOXM1 leads to an increase in ROS, resulting in neutrophil extracellular trap (NET) formation, leading to tissue damage and impaired healing (10). Therefore, FOXM1 serves an important role in the complications of diabetes and may be a new target for the prevention and treatment of diabetic complications.

FOXM1 is involved in DN. DN is a renal microvascular complication caused by DM, characterized by proteinuria and progressive renal injury, and is a key contributor to end-stage renal disease (74-76). The most typical pathological changes in renal biopsies of patients with DN are glomerular lesions, primarily including diffuse and nodular thylakoid expansion and glomerular basement membrane thickening (77).

FOXM1-activated sirtuin (SIRT)4 inhibits NF-κB signaling and NLRP3 inflammatory vesicles to attenuate renal injury and podocyte apoptosis in diabetic kidney disease (14). The overexpression of FOXM1 improves renal function and decreases pathological changes in mice, and it increases the expression of the foot cell marker nephrin in kidney tissue. In *in vitro* experiments, FOXM1 increases the viability and decreases pyroptosis of high Glucose-treated MPC5

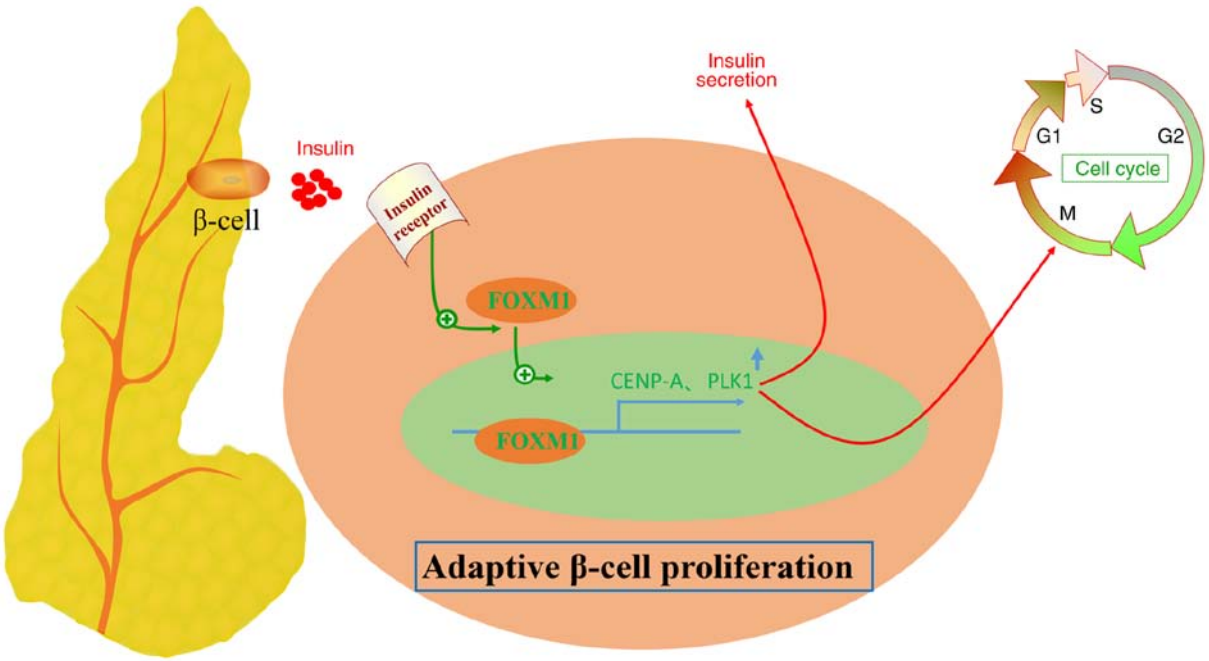

Figure 2. FOXM1/PLK1/CENP-A pathway enhances adaptive β-cell proliferation. Adaptive β-cell proliferation contributes to the maintenance of functional β-cell mass in mice and humans. Growth factor signaling regulates mitotic cell cycle progression via the FOXM1/PLK1/CENP-A pathway, a critical component in the β-cell adaptive response. FOXM1, forkhead box M1; PLK1, Polo-like kinases; CENP-A, centromere protein A.

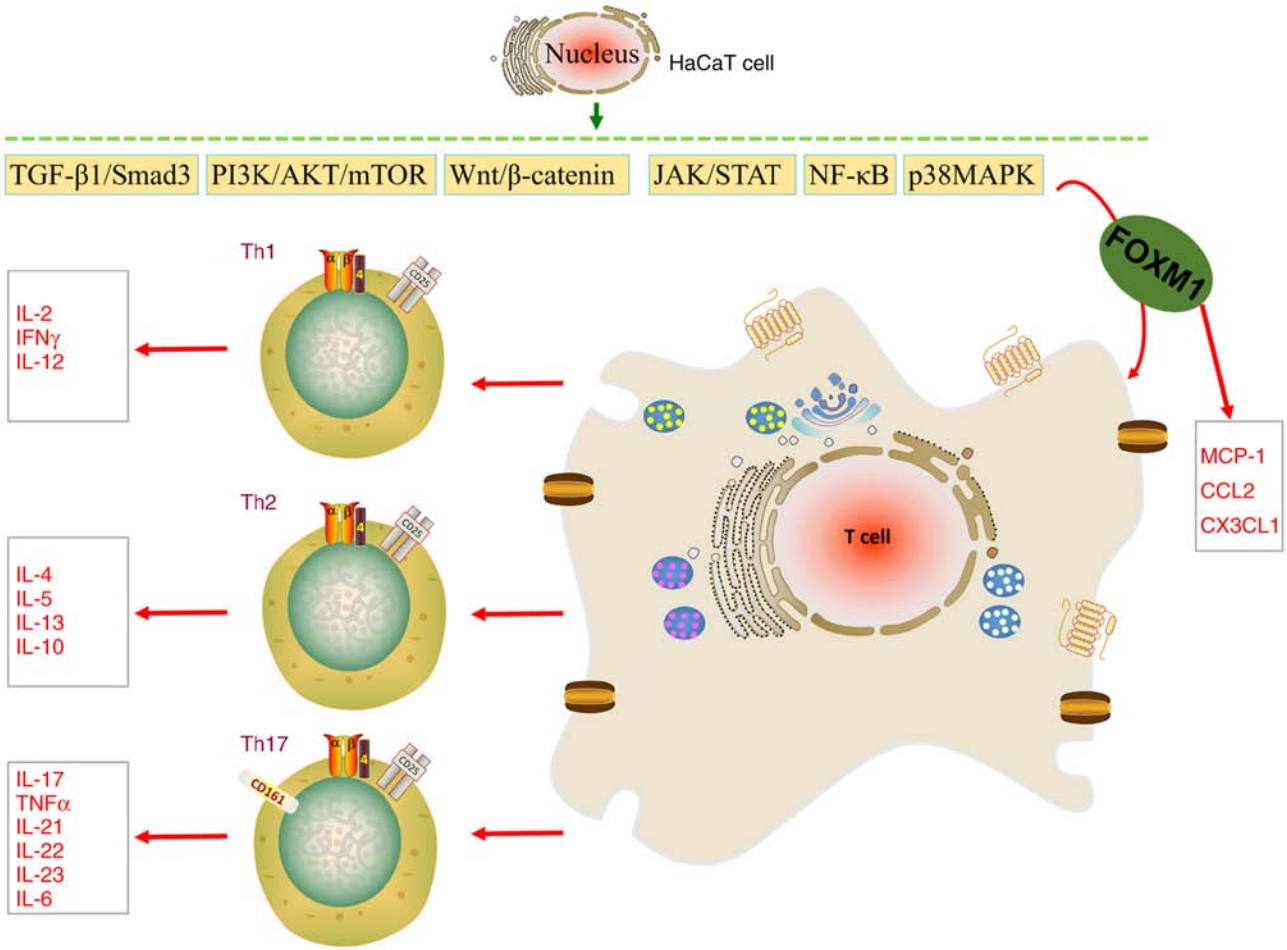

Figure 3. FOXM1 is involved in regulation of diabetes-related inflammatory responses. FOXM1 is involved in the pathogenesis of diabetes by regulating the expression of inflammation-associated mediators IL-1, IL-6, TNF-α, and cytokines MCP-1, CCL2, and CX3CL1. In addition, FOXM1 regulates certain inflammation-related signaling pathways, such as Wnt/β-catenin, JAK/STAT, NF-κB, TGF-β1/Smad3, PI3K/AKT/mTOR and P38MAPK. FOXM1, forkhead box M1; MCP-1, monocyte chemotactic protein-1; CCL2, chemokine (C-C motif) ligand 2; CX3CL1, C-X3-C motif chemokine ligand 1; Th, T helper.

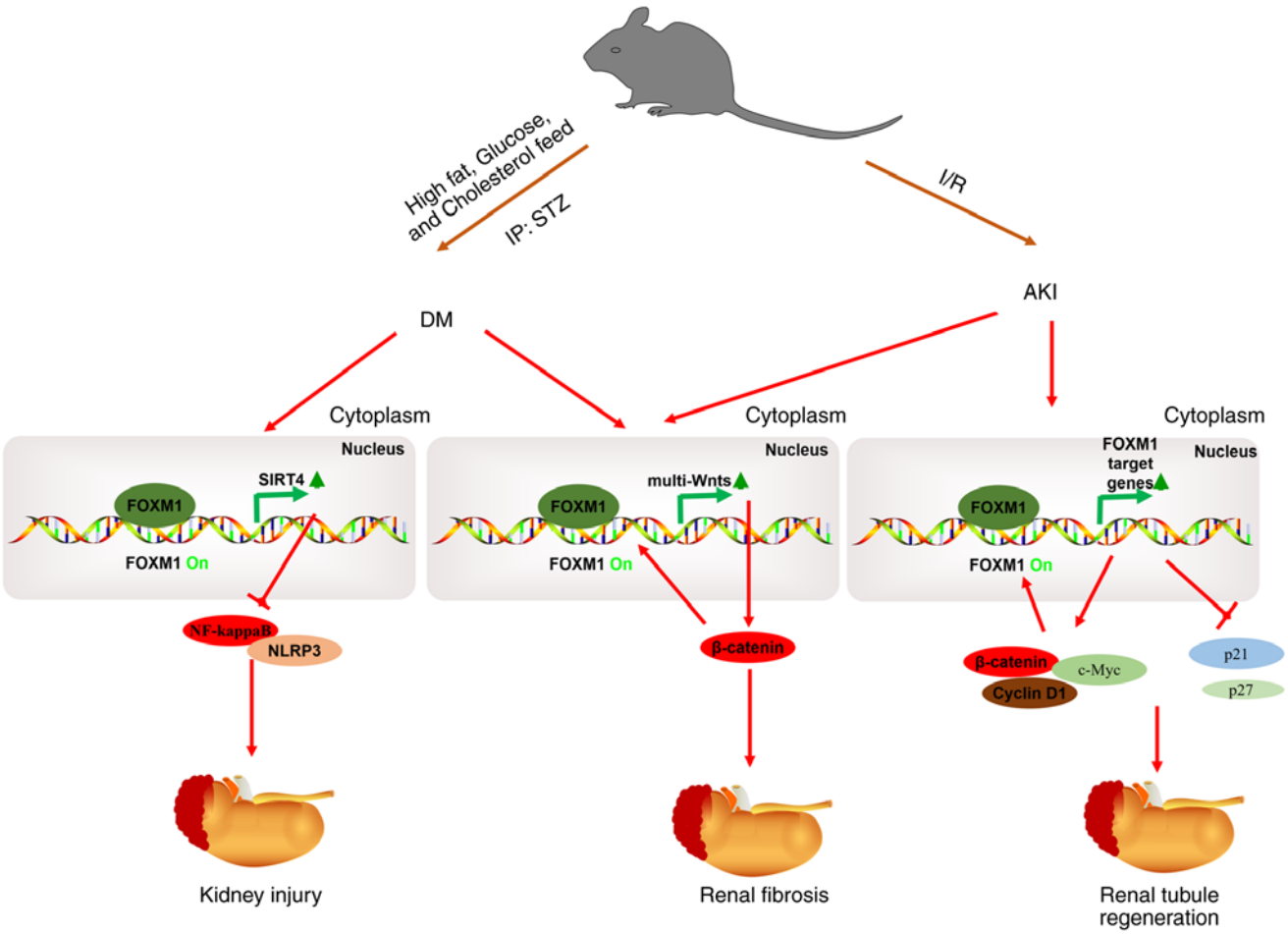

Figure 4. FOXM1 may be involved in diabetic nephropathy by regulating signaling pathways such as NF-κB/NLRP3 and Wnt/β-catenin. FOXM1 inhibits diabetic kidney injury by regulating expression of SIRT4 and promotes diabetic kidney tissue repair. FOXM1 activates β-catenin, Cyclin D1 and c-myc genes, inhibits the expression of p21 and p27 and induces metanephric tubule regeneration. FOXM1, forkhead box M1; SIRT4, sirtuin; IP, intraperitoneal; STZ, streptozotocin; I/R, ischemia reperfusion; AKI, Acute kidney injury.

cells and increases the expression of the podocyte marker nephrin, while decreasing the expression of NLRP3 inflammatory vesicles and cleaved caspase 1 associated with scorch death (14). In conclusion, FOXM1 alleviates renal injury and podocyte pyroptosis in patients with DN by transcriptionally activating SIRT4 and inhibiting the NF-κB signaling pathway and NLRP3 inflammatory vesicles (Fig. 4).

Activation of the Wnt/β-catenin pathway serves a key role in promoting renal fibrosis. The transcription factor FOXM1 is significantly increased in the kidney of patients with obstructive kidney and fibrosis (64). FoxM1 is mainly distributed in the renal tubular epithelial cells. In renal tubular epithelial cells, overexpression of FoxM1 promotes the expression of eight Wnts, whereas knockdown of FoxM1 inhibits angiotensin II)-induced expression of multiple Wnts, including Wnt1, Wnt2b and Wnt3, and FoxM1 regulates the transcription of Wnt1, Wnt2b, and Wnt3. Inhibition of FoxM1 downregulates expression of Wnts, ultimately leading to the reduction of renal fibrosis (64). These findings suggest that FoxM1 may be a key switch in activating the β-catenin pathway and renal fibrosis (Fig. 4). Therefore, FoxM1 may be a potential therapeutic target for the renal fibrosis (64).

Acute kidney injury (AKI) is characterized by sudden loss of renal function due to tubular epithelial damage. Renal tubular regeneration is essential to prevent progression of chronic kidney disease (78). Renal FoxM1 expression is increased in mice following renal ischemia/reperfusion (I/R)-induced AKI. Thiostrepton targeting of FoxM1 decreases FoxM1-regulated pro-proliferative factors and cell proliferation *in vitro*, as well as tubular regeneration in mice following AKI, indicating FoxM1 is important for tubular regeneration after AKI (78). FOXM1 inhibits diabetic kidney injury and promotes tissue repair by regulating SIRT4 expression; FOXM1 activates β-catenin, Cyclin D1 and c-myc, and inhibits p21 and p27 expression to induce tubular regeneration after AKI. In addition, FOXM1, induced early in injury, is required for epithelial cell proliferation *in vitro*, and is dependent on epidermal growth factor receptor (EGFR) stimulation (79).

FOXM1 regulates multiple signaling pathways and gene expression, including TGF-β, Wnt/β-catenin and NF-κB (64,80,81), as well as cell cycle, apoptosis and oxidative stress (82,83). Thus, it affects the proliferation, apoptosis and differentiation of cells, including glomerular and tubular cells (81). Therefore, FOXM1 may be a new target for treatment of DN. Researchers are exploring the signaling pathways and mechanisms of action regulated by FOXM1, as well as potential FOXM1 application in DN diagnosis and treatment (64,80-83).

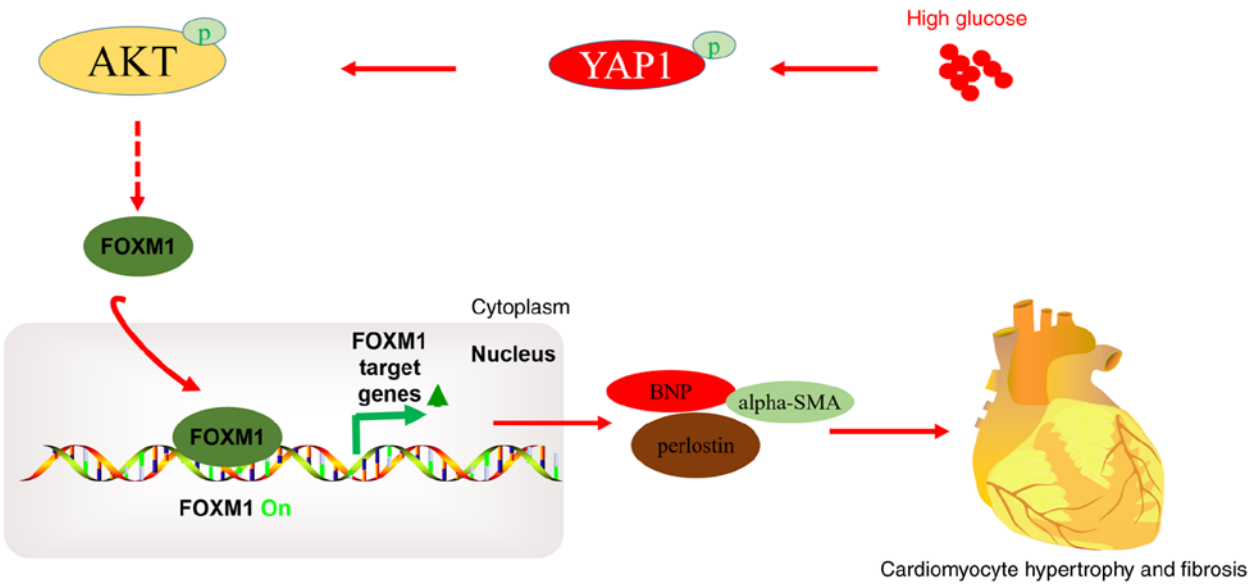

Figure 5. Schematic diagram of the signaling pathway of YAP1/FOXM1 activity in the induction of cardiomyocyte hypertrophy and fibrosis. Under hyperglycemia stress, YAP1 is activated in cardiomyocytes following reduced inactivating phosphorylation of YAP1. High glucose also increases activation of YAP1. Elevated YAP1 leads to increased AKT phosphorylation, thus promoting AKT activity. Increased AKT mediates inactivation of FOXM1. Upregulated YAP1 leads to aberrant FOXM1 accumulation within the cardiomyocyte. This elevated FOXM1 promotes pathological remodeling of cardiomyocytes, leading to cardiomyocyte hypertrophy and fibrosis. YAP, Yes-associated protein 1; FOXM1, forkhead box M1; p, phosphorylated; BNP, brain natriuretic peptide; SMA, smooth muscle actin.

FOXM1 may be involved in regulation of DR. Oxidative stress and inflammation are key causative factors for DR, which is the most common ocular complication of DM and the leading cause of visual impairment in working-age people worldwide. FOXM1 regulates cell cycle, proliferation, apoptosis and metabolism by affecting the expression of microvascular cell inflammation (IL-1β, IL-6, TNF-α and NF-κB) and apoptosis genes (caspase-3) and may be involved in the regulation of DR. INS blocking leads to elevated blood sugar levels and may lead to excess triggering of FOXM1, ultimately increasing the production of several apoptotic and inflammatory factors such as TNF-α and NF-κB, as well as ROS, which may also lead to DR (16,20,23,66).

FOXM1 can regulate the expression of retinopathy-related genes such as VEGF and TGF-β, thereby affecting the occurrence and progression of DR (84-87). Therefore, FOXM1 may serve an important role in the occurrence and development of DR. To the best of our knowledge, however, there are no studies on the regulatory role of FOXM1 in DR.

FOXM1 is involved in diabetic neuropathy. Diabetic neuropathy is a common complication that affects function of the nervous system, including sensory, motor and autonomic systems (42). By blocking the hepatic branch of the vagus nerve and inducing deletion or overexpression of hepatocyte-specific FOXM1, it has been shown that vagal signaling is involved in the inhibition or rapid activation of the hepatocyte FOXM1 pathway and affects hepatocyte proliferation following partial hepatectomy. Vagotomy increases postoperative mortality and replenishment of hepatic FOXM1 prevents this, which is a key mechanism to improve survival following liver injury. Notably, macrophages act as mediators of vagal signaling and acute activation of the FOXM1 pathway in hepatocytes (27). Acetylcholine secreted by the vagus nerve and IL-6 secreted by macrophages are involved in the molecular mechanism of vagus-macrophage-hepatocyte transduction by which STAT3 is phosphorylated via the IL-6 signaling pathway and phosphorylated STAT3 binds to the FOXM1 gene promoter, and the activated FOXM1 gene promotes hepatocyte regeneration (27,88). Vagal signaling directly activates the FOXM1 pathway in pancreatic β cells, thus promoting compensatory proliferation (42,89). Unlike islet cells, which are abundantly distributed, vagus innervation is scarce in the liver and only visible around the portal vein area. Thus, vagal signaling-mediated IL-6 production in hepatic macrophages upregulates hepatocyte FOXM1, leading to liver regeneration and ensuring survival. This complex multi-step mechanism of neuronal, immune and parenchymal cells allows emergency regenerative signals to be amplified and propagated through the organ, thus promoting rapid liver regeneration and ensuring systemic survival following severe liver injury (27,88,89). Studies suggest that FOXM1 may be involved in development and progression of diabetic neuropathy through mechanisms such as regulation of neuronal apoptosis, oxidative stress and inflammation (27,42,88,89). However, more studies are needed to determine the exact role and mechanisms of FOXM1 in diabetic neuropathy.

FOXM1 is involved in diabetic cardiovascular disease. FOXM1 is involved in the development and progression of diabetic cardiovascular disease. During diabetes, sustained hyperglycemic stress in cardiac primary contractile cells and cardiomyocytes leads to increased apoptosis, which leads to cardiomyocyte hypertrophy and fibrosis (90). Cardiac hypertrophy and fibrosis lead to structural and functional abnormalities (such as arrhythmia, heart failure and atrial fibrillation) that contribute to risk of heart failure. FOXM1 is overexpressed in myocardial tissue during hyperglycemia, leading to increased cardiomyocyte hypertrophic and fibrotic responses (11) (Fig. 5). Under hyperglycemic stress, YAP1

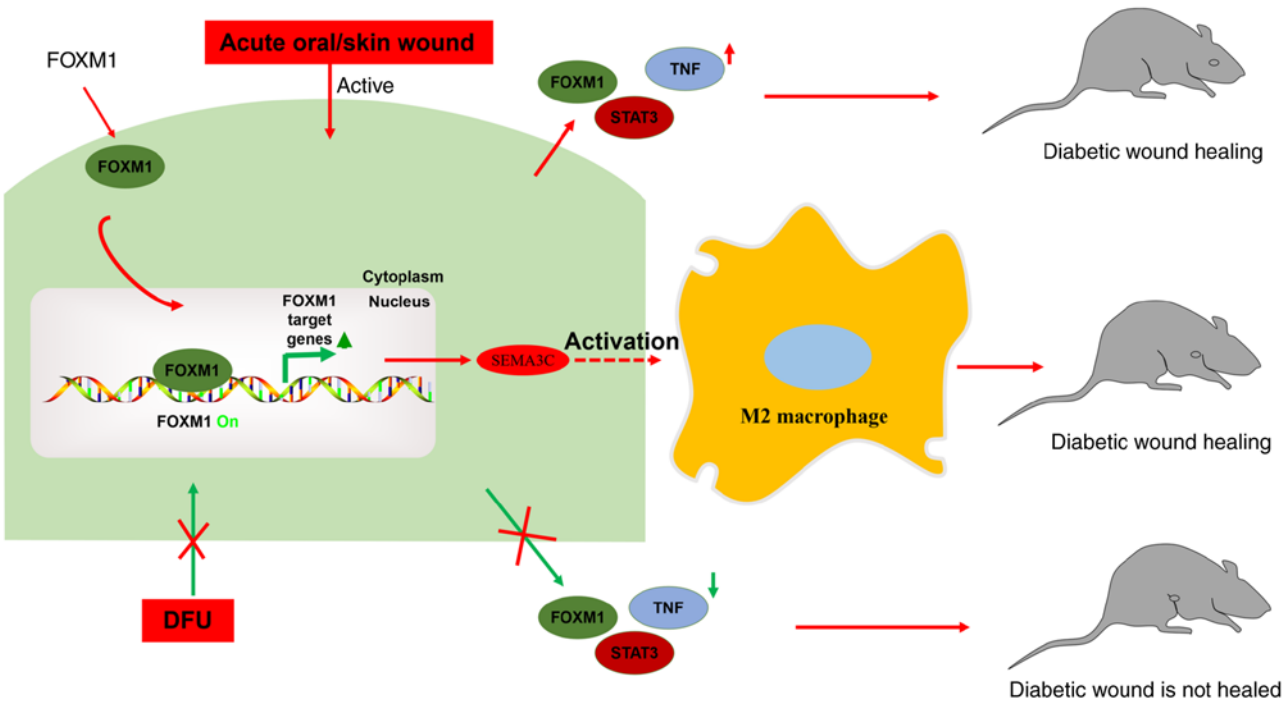

Figure 6. Molecular mechanisms of FOXM1-mediated inflammatory factors (SEMA3C, STAT3, TNF) in undamaged oral mucosa, skin and DFUs models. FOXM1 activates transcription of SEMA3C, thus enhancing M2 polarization, which accelerates wound healing in DFU. FOXM1 demonstrates a similar wound-activated signature of genes involved in differentiation, cytokines and intermediate filaments. Inhibition of FOXM1, STAT3 and TNFα regulators results in lack of immune-cell activation, proliferation and survival in DFU, contributing to dysregulated inflammatory response and inhibition of wound healing. FOXM1, forkhead box M1; SEMA3C, semaphorin 3C; DFU, diabetic foot ulcer.

in cardiomyocytes leads to elevated AKT phosphorylation by activating YAP1, and elevated AKT mediates loss of inhibitory regulation of FOXM1 by GSK3β inactivation. Thus, upregulated YAP1 leads to abnormal FOXM1 accumulation in cardiomyocytes. This elevated FOXM1 promotes pathological remodeling of cardiomyocytes, leading to cardiomyocyte hypertrophy and fibrosis. FOXM1 serves an important role in cardiovascular pathology (11). FOXM1 may promote the development of diabetic cardiovascular disease. Endothelial and smooth muscle cells mediate vascular remodeling via FoxM1 signaling interactions (91); FOXM1 promotes vascular endothelial cell and cardiomyocyte proliferation and neonatal heart regeneration (92). FOXM1 may also be involved in the development of diabetic cardiovascular disease. FOXM1 can regulate cardiomyocyte proliferation and thus affect cardiomyocyte survival and function. During zebrafish heart regeneration following injury, Foxm1 is required in cardiomyocyte proliferation through transcriptional regulation of cell cycle genes (32). FOXM1 regulates biological processes such as cardiac fibrosis and inflammatory responses, accelerating the deterioration of cardiac function (11). Previous studies have shown that FOXM1 serves a key role in inflammation and inflammatory cell recruitment (10,14,15). FOXM1 regulates the expression of pro-inflammatory cytokines and chemokines, including IL-6, inducible nitric oxide synthase (INOS), Chemokine C-C-Motif Receptor 2 (CCR2) and CX3C chemokine receptor1 (CX3CR1) (93-96).

ERK acts upstream of the FOXM1 transcription factor, which is a key downstream effector of the ERK pathway involved in the control of cycle progression and cell proliferation and activates it via phosphorylation and nuclear translocation. FOXM1 expression is induced by tissue damage and is decreased in senescent cells (97,98). Therefore, FOXM1 is associated with the pathogenesis of atherosclerosis and may be involved in diabetic atherosclerosis (13).

Hyperglycemia, a feature of diabetes, can induce vascular complications by increasing endothelial cell apoptosis and limiting proliferation. The potential role of FoxM1 in high-glucose-induced EC injury, where FoxM1 protects EC from high-glucose-induced growth arrest and apoptosis by inhibiting ROS induced by regulation of the Akt and ERK pathways, may be a novel therapeutic target to treat EC dysfunction (12). Therefore, the role of FOXM1 in diabetic cardiovascular disease may serve as a targets and strategies for the prevention and treatment of diabetic cardiovascular disease.

FOXM1 is involved in DFU. DFU is a serious complication caused by DM, associated with decreased quality of life and high mortality, with deterioration leading to foot amputation (99-101). FOXM1 controls oxidative stress by inducing the expression of ROS (such as Superoxide dismutase (SOD2, glutathione peroxidase 4, Serine/threonine protein phosphatase, Glycerol phosphate dehydrogenase, Serine hydroxymethyltransferase 2 and Methylene tetrahydrofolate dehydrogenase 2) (57,102). The wound environment of DFU is accompanied by prolonged inflammation, leading to impaired wound healing. FOXM1 is lowly expressed in DFU rat wound tissue and its ability to enhance DFU macrophage 2 (M2) polarization and trauma healing is enhanced; silencing FOXM1 reverses promotion of M2 polarization-induced human dermal fibroblast proliferation and migration (Fig. 6).

Thus, targeting the transcription factor FOXM1 may provide a therapeutic target for promoting DFU wound healing (15).

In a diabetic mouse model of skin injury, inhibition of FOXM1 results in delayed wound closure and decreased recruitment of neutrophils and macrophages (9). FOXM1 is a regulator of neutrophil response during acute skin and oral mucosal wound healing in human DFU (9).

The FOXM1 signaling pathway regulates NET formation during diabetic wound healing. FOXM1 is a regulator of NET formation by modulating ROS levels to promote neutrophil immune responses during wound healing (103,104). Furthermore, triggering receptor Expressed on Myeloid cells 1 (TREM1) is associated with FOXM1 during DFU wound healing, and TREM1 activation increases the recruitment of FOXM1-positive neutrophils and enhances diabetic wound healing (10,105). FOXM1 is downregulated in DFU, resulting in decreased neutrophil response, suggesting that TREM1/FOXM1 is a key regulator of diabetic wound healing. TREM1 promotes wound healing by regulating Interlukin-1β (IL1B), IL6, Cyclin Dependent Kinase 1 (CDK1), Amphiregulin (AREG), SOD2 and C-X-C motif chemokine 8 (CXCL8) which promote FOXM1 gene activation (10). TREM1/FOXM1 promotes the recruitment of neutrophils, reverses the effects of diabetes, and promotes wound healing *in vivo,* suggesting that the FOXM1 pathway is a novel regulator of NET formation during diabetic wound healing and revealing a new therapeutic strategy to promote DFU healing (10).

The expression of FOXM1, GAS5 and SDF4 is decreased in the skin tissue of patients with DFU (31). High glucose stimulation induces endoplasmic reticulum stress and apoptosis, which inhibits angiogenesis in Human umbilical vein endothelial cells (HUVECs), whereas FOXM1 overexpression alleviates inhibition of angiogenesis. FOXM1 regulates GAS5 expression and knockdown of GAS5 reverses the effects of FOXM1 overexpression. FOXM1 inhibits endoplasmic reticulum stress and apoptosis and promotes angiogenesis by mediating the GAS5/TAF15/SDF4 axis generation, providing a novel molecular mechanism for the treatment of DFU (31).

FOXM1 is involved in diabetic patients with tumors. Epidemiological studies have shown that DM and hyperglycemia are not only risk factors (106), but also poor prognostic indicators for numerous types of cancer (such as kidney, oesophageal, colorectal, breast and bladder cancer, and leukaemia) (107,108). A previous study found that high glucose-induced KKU-213A and KKU-213B cells exhibit high FOXM1 expression in a dose-dependent manner (22).

Obesity and inflammation are associated with increased risk of hepatocellular carcinoma, which is the leading cause of cancer-associated deaths worldwide. Tissue metalloproteinase inhibitor 3 (Timp3) deficiency during hepatocarcinogenesis in obesity is associated with decreased FoxM1 transcriptional activity via the H19/microRNA (miR)-675/p53 pathway (109). Timp3 ablation leads to cell cycle perturbation by suppressing FoxM1 transcriptional activity through the H19/miR-675/p53 pathway (109). Investigators have designed antitumor and antidiabetic drugs targeting FOXM1 (17,110).

Studies have identified that FOXM1 serves a key role in INS secretion and islet cell proliferation and thus FOXM1 inhibitors may be useful in improving IR and glycemic control (18,25,29,36,37,111,112). FOXM1 inhibitors include thiostrepton and siomycin A, which inhibit FOXM1 transcriptional activity in cellular and animal models (17,110). However, further studies are needed to validate the efficacy and safety of inhibitors for use in clinical therapy.

5. Conclusion

DM and its complications are a notable public health problem worldwide and impact quality of life and survival of patients. FOXM1 is an important transcription factor that has been shown to serve a key role in the development and progression of DM and its complications (9,10,15,31). The present study reviewed the role and function of FOXM1 in diabetes and its complications. FOXM1 serves an important role in INS secretion and resistance (112). FOXM1 can promote INS synthesis and secretion, while inhibiting IR. In addition, FOXM1 affects the balance of glucose metabolism by regulating expression of genes associated with glucose metabolism. Second, the role of FOXM1 in diabetic complications has also received attention. Studies have shown that FOXM1 can be involved in occurrence and development of diabetes-associated complications such as nephropathy, neuropathy, and retinopathy (9-31). FOXM1 affects the occurrence and development of diabetic complications by regulating biological processes such as cell proliferation, apoptosis, and oxidative stress. Further research is needed to determine the specific regulatory mechanism of FOXM1, interaction with other transcription factors and the role of FOXM1 in different types and stages of diabetes. Future studies should investigate the role and function of FOXM1 in diabetes and its complications to provide novel approaches for the prevention and treatment of diabetes.

Despite need for effective treatments to cure diabetic complications such as DFU, no new Food and Drug Administration-approved therapy has been effective since 1998. The pathogenesis of diabetic complications involves intrinsic factors, such as neuropathy, vasculopathy, ischemia, infection, fibrosis and immune dysfunction. In conclusion, further development of drugs for the treatment of diabetes and its complications is required.

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Availability of data and materials

Not applicable.

Authors' contributions

ZZ, DZ and XL designed the study and wrote the manuscript. BZ, ML, YS, SS and WQ performed the literature review. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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