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FoxO Transcription Factors and Regenerative Pathways in Diabetes Mellitus

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Abstract

Mammalian forkhead transcription factors of the O class (FoxO) are exciting targets under consideration for the development of new clinical entities to treat metabolic disorders and diabetes mellitus (DM). DM, a disorder that currently affects greater than 350 million individuals globally, can become a devastating disease that leads to cellular injury through oxidative stress pathways and affects multiple systems of the body. FoxO proteins can regulate insulin signaling, gluconeogenesis, insulin resistance, immune cell migration, and cell senescence. FoxO proteins also control cell fate through oxidative stress and pathways of autophagy and apoptosis that either lead to tissue regeneration or cell demise. Furthermore, FoxO signaling can be dependent upon signal transduction pathways that include silent mating type information regulation 2 homolog 1 (*S. cerevisiae*) (SIRT1), Wnt, and Wnt1 inducible signaling pathway protein 1 (WISP1). Cellular metabolic pathways driven by FoxO proteins are complex, can lead to variable clinical outcomes, and require in-depth analysis of the epigenetic and post-translation protein modifications that drive FoxO protein activation and degradation.

Keywords

Akt; apoptosis; autophagy; β-catenin; caspase; CCN; diabetes mellitus; epigenetic; erythropoietin; forkhead; FoxO; metabolism; nicotinamide; oxidative stress; sirtuins; SgK; SIRT1; stem cells; WISP; Wnt

1. Diabetes Mellitus: Clinical Implications

Diabetes mellitus (DM) is a devastating disease that can involve any system of the body (1, 2). In the nervous system, DM can result in cerebral ischemia stroke (3-8), retinal disease (9-12), peripheral nerve disorders (13, 14), dementia such as Alzheimer's disease (15-18), and psychiatric disorders (19, 20). Vascular disease can be mediated by DM and result in endothelial cell senescence (21), injury to endothelial cells (22-28), cardiovascular disease (29-37), atherosclerosis (8, 38-40), platelet dysfunction (3, 41), loss of endothelial progenitor cells (42-47), and impaired angiogenesis (27, 35, 48). Given the broad disorders that can be a result of DM in the nervous and cardiovascular systems, it comes as no surprise

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that DM can have profound negative effects on the immune system (36, 49-55), renal function (56-60), hepatic metabolism (13, 61-66), and musculoskeletal integrity (38, 67-70).

The incidence of DM is increasing throughout the world (71). Approximately 350 million individuals currently have DM, but the World Health Organization estimates that DM will be the seventh leading cause of death by the year 2030 (72). In developed countries such as the United States that have an estimated 21 million individuals with DM (73), it is surprising to learn that another 8 million individuals are believed to suffer from metabolic disorders but remain undiagnosed (12, 74, 75). Costs to care for individuals with DM are significant. Almost $9,000 USD are spent in the United States for each individual with DM per year and overall care for patients with DM consumes 17% of the Gross Domestic Product (76).

2. Cellular Injury with Diabetes Mellitus

At the cellular level, a significant mediator that leads to injury during DM involves oxidative stress and the release of reactive oxygen species (ROS) (8, 13, 77-80). Several genetic polymorphisms in oxidative stress pathways have recently been linked to the complications of DM (81). Agents that can promote the complications of DM, such as advanced glycation end products (AGEs) (30), result in the release of ROS, caspase activation (47, 82-84), and loss of anti-oxidant levels (85). In the nervous system, oxidative stress during DM can affect cognition (86), behavior (19), retinal nerve function (25), and brain mitochondria (52, 87-91). In the cardiac system, oxidative stress during DM can be responsible for cardiomyopathy (37, 92), myocardial infarction and re-perfusion injury (93), cardiomyocyte injury (94), and fibrosis (37). Vascular cell and endothelial cell dysfunction occurs during DM through oxidative stress pathways that involve impairment of stem cell and progenitor cell mobilization (42, 44), endothelial senescence (21), inhibition of angiogenesis (48), vascular aging (95), and endothelial cell injury (22-24, 46, 96-98). Pancreatic human islet cells also are susceptible to oxidative stress injury during DM (99, 100) and high lipid exposure (101). In clinical studies, poor glycemic control in DM patients can lead to the depression of endothelial progenitor cell levels (43). Patients with DM have serum markers of oxidative stress with ischemia-modified albumin (102).

During oxidative stress with DM, cell death can result from programmed cell death pathways of autophagy and apoptosis. Apoptosis has both an early phase that involves the externalization of plasma membrane lipid phosphatidylserine (PS) residues and a subsequent phase that consists of genomic DNA degradation (103-105). Macrophages and microglia can be prevented from engulfing otherwise functional cells that are tagged with PS residues by blocking membrane PS externalization (2, 106, 107). The later phase of apoptosis with DNA destruction is not readily reversible (108-113). In experimental studies with diabetic rats, elevated glucose can lead to oxidative stress and apoptotic injury in areas of the prefrontal cortex of the brain (19). Hyperglycemia not only leads to endothelial senescence, but also results in the presence of apoptotic makers and cell death on endothelial cells (21, 23, 96, 97). Elevated glucose in diabetic mice can injure pancreatic islet cells and lead to apoptotic cell death (99).

In reference to autophagy, this is a process that removes non-functional organelles and recycles cytoplasmic components to remodel tissue (105, 114-117). During macroautophagy, cytoplasmic proteins and organelles are sequestered into autophagosomes and then combined with lysosomes for degradation and are recycled for future cellular processes (32, 46, 71, 118, 119). Under some circumstances, autophagy may protect cells during DM by eliminating non-functional organelles and may be less of a significant mediator of cell injury (120). Autophagy removes misfolded proteins and eliminates non-functioning mitochondria to prevent β-cell dysfunction and the onset of DM (121). Autophagy has been reported to improve insulin sensitivity during high fat diets in mice (69). Exercise in murine models can foster the induction of autophagy and regulate glucose homeostasis (122). Loss of autophagy with haploinsufficiency of an essential *Atg7* gene in murine models of obesity results in increased insulin resistance with elevated lipids and inflammation (118). It is important to note that autophagy and apoptosis are closely tied in DM to influence cell survival. Autophagy may protect cardiomyocytes from apoptotic cell death during DM (32).

Autophagy has a detrimental side during DM (123). Increased activity of autophagy can result in the loss of cardiac and liver tissue in diabetic rats during diet modification in attempts to achieve glycemic control (64). AGEs lead to atherosclerosis (38) and cardiomyopathy (92) through the induction of autophagy. Autophagy has been reported to injure endothelial progenitor cells, promote mitochondrial oxidative and endoplasmic reticulum stress (124), and block angiogenesis (46) during exposure to elevated glucose.

3. Targeting Forkhead Transcription Factors of the “O” Class

Mammalian forkhead transcription factors assigned to the O class represent a novel target for drug development to treat metabolic disorders and DM (125, 126) (Table 1). Mammalian FOXO proteins, FOXO1, FOXO3, FOXO4, and FOXO6 (127), have a butterfly-like appearance on X-ray crystallography (128) and nuclear magnetic resonance (129). The forkhead box (FOX) family of genes has a conserved forkhead domain described as a “winged helix” (130). In regards to nomenclature, all letters are capitalized for human Fox proteins (131). Only the initial letter is listed as uppercase for the mouse and for all other chordates the initial and subclass letters are in uppercase (34, 113, 132, 133).

FoxO proteins are found throughout the body. In regards to metabolic signaling, FoxO proteins are conserved among multiple species that include *Caenorhabditis elegans*, *Drosophila melanogaster*, and mammals. FoxO proteins are homologous to the transcription factor DAuer Formation-16 (DAF-16) in the worm *Caenorhabditis elegans*. DAF-16 can determine metabolic insulin signaling and lead to lifespan extension (134, 135).

Both epigenetic (7, 136, 137) and post-translation protein modifications regulate the function of FoxO proteins. FoxO proteins are modified by phosphorylation (22, 97, 138-147), acetylation (137, 138, 148), and ubiquitylation (24, 52, 149, 150) (Table 1). Phosphorylation of FoxOs can occur through the serine-threonine kinase protein kinase B (Akt) (54, 75, 151-155) and the serum- and glucocorticoid-inducible protein kinase (SgK) (156). Akt and SgK phosphorylate FoxO proteins at different sites affording various

pathways to control FoxO protein activity (157). Kinases such as Akt phosphorylate FoxO proteins to foster binding to 14-3-3 proteins in the cell cytoplasm, prevent nuclear translocation of FoxOs, and then block the transcription of target genes that promote apoptosis (141, 145, 158, 159). Yet, the phosphorylation site of FoxO proteins by specific protein kinases can be important in determining the activity of forkhead transcription factors. For example, mammalian sterile 20-like kinase-1 can phosphorylate FOXO proteins, disrupt the binding to 14-3-3, and allow nuclear translocation of FOXO to promote apoptotic cell death (160).

Similar to post-translational phosphorylation of FoxO proteins, ubiquitylation and acetylation are also vital counterparts to modulate activity of FoxO proteins (35, 161). Ubiquitination and the degradation of FoxO proteins can be fostered through the silent mating type information regulation 2 homolog 1 (*S. cerevisiae*) (SIRT1) (148, 162, 163). SIRT1 can oversee stem cell development (5, 164) and protect cells through the inhibition of FoxO activity (53, 148, 165-167). FoxOs can bind to the SIRT1 promoter region that contains a cluster of five putative FoxO core binding repeat motifs (5 x insulin receptor substrate (IRS-1)) and a forkhead-like consensus-binding site (FKHD-L) to promote SIRT1 transcription (168). FoxO proteins can then regulate SIRT1 transcription and increase SIRT1 expression (168). SIRT1 promotes FoxO-driven SIRT1 autotranscription through the activation and deacetylation of FoxOs (169). Akt also results in the ubiquitination and degradation of FoxOs through the 26S proteasome of FoxO proteins (170, 171). In relation to acetylation, FoxO proteins are acetylated by histone acetyltransferases that include p300, the CREB-binding protein (CBP), and the CBP-associated factor (172). Once acetylated such as by CBP, FoxO proteins translocate to the cell nucleus but have diminished activity since acetylation of lysine residues on FoxO proteins can limit the ability of FoxO proteins to bind to DNA (173). Acetylation can increase phosphorylation of FoxO proteins mediated through Akt (173). FoxO proteins are deacetylated by histone deacetylases, such as SIRT1 (170, 174-176). Histone deacetylase 2 (HDAC2) also forms a physical complex with FoxO3a to affect FoxO3a-dependent gene transcription and oxidative stress-induced cell death (137).

4. FoxO proteins, Oxidative Stress, Apoptosis, and Autophagy

FoxO proteins play a critical role in cell survival and regeneration (Table 1). FoxO proteins may have different effects upon cell survival during oxidative stress with FOXO1 preventing oxidative stress damage and FOXO3a promoting oxidative cell death in systems that involve the maternal decidua (177). Under some conditions, the activation of FoxO proteins may prevent apoptotic cell injury during oxidative stress such as in chondrocytes (178). The conditional deletion of FoxO1, FoxO3a, and FoxO4 in mouse hematopoietic stem cells may be detrimental and lead to an increase in ROS (179). In addition, FoxO3a may be necessary with other pathways for rejuvenating the function of mesenchymal stem cells (180).

FoxO proteins can lead to the induction of autophagy and increase cell survival (Table 1). In experimental models of full-length mutant Huntingtin (mHtt) transgenic mice, ectopic expression of FoxO1 leads to autophagy and the clearance of toxic mHtt protein in neurons

(181). Expression of a constitutively active form of FoxO3 increases human articular chondrocyte cell viability and the expression of autophagy related proteins (178). SIRT1-mediated deacetylation of FoxO1 leads to starvation-induced increases in autophagic flux that maintain left ventricular function during periods of starvation (182). Cardiac expression of constitutively active FoxO3 reverses heart atrophy through the activation of autophagic pathways (183). Yet, FoxO cell protection may not always be directly tied to the induction of autophagy. Up-regulation of FoxO3 and SIRT1 with a reduction in autophagy occurs in human bronchial epithelial cells exposed to cigarette smoke condensates in the presence of the anti-oxidant Amurensis H (Vam3), a dimeric derivative of resveratrol, that can reduce oxidative stress (184).

With apoptotic cell death, FoxO proteins promote membrane PS externalization and DNA degradation to lead to cell injury (185, 186). Endothelial cell dysfunction occurs with a reduction in SIRT1 expression and an increase in FoxO1 expression during exposure to elevated glucose (21). Several studies support a detrimental role for FoxO proteins that can lead to cell injury. For example, inhibition or gene knockdown of FoxO1 or FoxO3a leads to protection against microglial cell injury during oxidative stress (187) and Aβ exposure (185), increased neuronal cell survival through nicotinamide adenine dinucleotide (NAD^+) precursors (140), growth factor protection with erythropoietin (EPO) (22, 139, 141, 162) and neurotrophins (188-190), protection against cerebral ischemia (159), and increased cell survival with metabotropic glutamate receptor activation (191). EPO can phosphorylate FoxO proteins, inactivate these proteins (75, 192), and lead to cellular protection in models of experimental DM and oxidative stress (22, 141, 193).

FoxO cell death pathways are dependent, in part, upon Wnt signaling (Table 1). Wnt signaling, including Wnt1 inducible signaling pathway protein 1 (WISP1), also known as CCN4 (194, 195), regulates cell development, vascular growth, immunity, cancer, stem cell proliferation (196-200) and cellular metabolism (25, 195, 198, 200). Wnt signaling may assist in wound healing during DM (200) and can prevent vascular injury during experimental DM (22, 23). Wnt signaling promotes cellular protection against apoptotic cell death through the inactivation of FoxO proteins. Phosphorylation and inhibition of FoxO3a activity by Wnt signaling β-catenin protects hepatocytes from apoptosis (143). Osteoblastic differentiation can be preserved in the presence of oxidative stress through the increased expression of Wnt signaling pathways and the inhibition of FoxO3a (201). Wnt signaling blocks apoptosis through the inhibition of FoxO3a activity to prevent cytochrome c release, Bad phosphorylation, and activation of caspases (186). WISP1 also can increase cell survival by limiting FoxO3a activity, blocking caspase 1 and 3 activation, and fostering SIRT1 nuclear trafficking (145). Growth factors such as EPO use Wnt signaling during experimental DM to block FoxO3a activity and increase endothelial survival (22).

Of note, FoxO regulation of Wnt signaling may be beneficial under other conditions. FoxO proteins can inhibit prostate cell malignant phenotypes by down-regulating Wnt signaling and β-catenin (202). The absence or loss of FoxO activity, such as through microRNA activity, may indicate an increased risk for cancer development (203) and promote tumor growth (204).

5. Pursuing Regenerative Pathways with FoxO for Diabetes Mellitus

In addition to impacting cellular survival and regeneration, FoxOs are important in regulating cellular metabolism and DM (34, 113, 125) (Table 1). Several studies suggest that inactivation of FoxO proteins may foster cytoprotection during DM. Insulin resistance may be resolved with the genetic deletion of hepatic FoxO1 (205). During exposure to high glucose in endothelial cells, FoxO1 is acetylated and leads to premature senescence that can be detrimental to vascular function (21). Activation of FoxO3a occurs during elevated glucose exposure that results in mitochondrial membrane depolarization, cytochrome c release, and caspase activation with subsequent apoptotic cell death (22, 24, 97). In mice, FoxO6 depletion can prevent diet-induced glucose intolerance and insulin resistance through inhibition of hepatic gluconeogenesis and limiting macrophage infiltration in the liver and adipose tissues (206). FoxO proteins can influence pancreatic β-cell survival as well. Thioredoxin-interacting protein (TXNIP) is necessary for β-cell survival. FoxO1 can bind to the TXNIP promoter, decreases TXNIP expression, and prevents TXNIP expression during the exposure to glucose (207). Retinal disease is prevented during therapies tied to FoxO3a inhibition in murine models of DM (208). In studies that examine the loss of SIRT1 with concurrent increased activity of Foxo1 in mice, insulin sensitivity is lost and overproduction of hepatic glucose leads to chronic hyperglycemia and increased ROS production (209). Models of diabetic nephropathy show that transforming growth factor-beta results in the nuclear exclusion of FoxO3a, blocks FoxO3a transcriptional activity, and protects renal mesangial cells from apoptosis (210). Enteric neurons can be protected from hyperglycemia by glial cell line-derived neurotrophic factor that activates Akt and inhibits FoxO3a activation (188). Mice overexpressing Foxo1 in skeletal muscle have impaired glycemic control and impaired skeletal muscle function (211).

Some clinical studies suggest a detrimental effect associated with forkhead transcription factors, body weight, and DM. A single nucleotide polymorphism in the 5′ flanking region of FOXO3a was associated with the greatest body mass index in individuals who were homozygous for the major allele of FOXO3a (212). Additional studies report that haplotype analyses of FOXO1a revealed that carriers of a specific haplotype had higher HbA_{1c} levels with increased mortality risk attributable to death from DM (213). Analyses with FOXO3a haplotypes demonstrate no differences in metabolic profile, fertility or fecundity, but an increased risk of stroke is present for specific Foxo3a haplotypes (213). Agents that control FoxO protein activity during metabolic disturbances may offer treatment for patients with DM. One potential agent to consider for the maintenance of cellular metabolism in DM is nicotinamide (52, 214-223). Nicotinamide can improve metabolic control in combination therapy (224), can be protective for pancreatic β-cell function (225), and reverses disease during diabetic peripheral neuropathy in animal models (226). Oral nicotinamide administration can protect β-cell function and prevent clinical disease in islet-cell antibody-positive first-degree relatives of Type 1 DM (225). Nicotinamide may be protective through the post-translational modification of FoxO3a. Nicotinamide can inhibit FoxO3a activity and preserve the integrity of the FoxO3a protein to block FoxO3a proteolysis that can yield pro-apoptotic amino-terminal fragments (140). It is important to discuss that prolonged exposure to nicotinamide in some studies has been reported to impair β-cell function and reduce cell

growth (227, 228). As a result, studies have shown a benefit with reduction in nicotinamide activity through nicotinamidases that degrade nicotinamide and lead to increased lifespan (215, 229-231).

However, in some sub-populations with specific haplotypes for FoxO1 and FoxO3, increased metabolic risk and disease from FoxO proteins in cardiovascular disorders may not occur (232). In fact, FoxO proteins may exert a beneficial effect during metabolic disorders under some conditions. FoxO proteins are homologous to DAF-16 that can regulate cellular metabolism and lifespan (149, 230, 233). FoxO proteins can stimulate the insulin-like growth factor binding protein-1 (IGFBP1) promoter by binding to a conserved insulin response sequence (234). Insulin and insulin-like growth factor-1 (IGF-1) can control and suppress this activity through activation of Akt (234, 235). Interferon-gamma driven expression of tryptophan catabolism by cytotoxic T lymphocyte antigen 4 can activate Foxo3a to protect dendritic cells from ROS generation in non-obese diabetic mice (236). In caloric restricted mice that have decreased energy reserves, mRNA expression in rat skeletal muscles is increased for specific Foxo proteins, suggesting that Foxo may have a protective function during metabolic disorders (237). In addition, FoxO1 expression leads to increased insulin signaling to regulate cellular metabolism in *Drosophila* and mammalian cells (238).

6. Future Considerations

DM affects multiple systems throughout the body leading to significant disability as well as death. New development of strategies targeting FoxO proteins may offer the opportunity to effectively provide clinical treatments for disorders of cellular metabolism and the clinical complications of DM. However, a number of hurdles must be overcome in consideration of the clinical utility of FoxO proteins. Further understanding of the pathways that determine injury in DM and the biological role of FoxO proteins are necessary to move forward. For example, how can cell death pathways of autophagy and apoptosis determine tissue injury during FoxO activation? Oxidative stress is a significant mediator of cell injury during DM. Under some conditions, autophagy can improve insulin sensitivity and regulate glucose homeostasis. FoxO proteins can lead to the induction of autophagy and enhance cell survival such that FoxO proteins reduce oxidative stress and assist with metabolic homeostasis. Yet, increased autophagy during DM may lead to the loss of tissue, may injure endothelial progenitor cells, and promote oxidative stress. Activation of FoxO proteins may prevent apoptotic cell injury during oxidative stress in some cell types. In other scenarios, it is the inhibition of FoxO protein activity that leads to cytoprotection that may require the activation of Wnt signaling pathways as well as SIRT1. Control of FoxO activity may be dependent upon a number of factors including the phosphorylation site of FoxO proteins by specific protein kinases that can determine whether FoxO proteins foster cell survival or conversely lead to cell death.

Furthermore, what are the factors that influence the ability of FoxO proteins to affect cellular metabolism? A number of studies suggest that inactivation of FoxO proteins may foster cytoprotection during DM, block insulin resistance, assist with pancreatic β-cell survival, and prevent immune cell tissue infiltration. Some clinical studies support a role to limit FoxO activity and decrease the risk of mortality from DM. In contrast, other clinical

work indicates that there is little or no association between increased metabolic risk and FoxO proteins. Other experimental studies suggest that increased FoxO protein expression is beneficial for insulin signaling and maintaining energy reserves. Epigenetic as well as post-translational modification of FoxO proteins during impairments in cellular metabolism may play an essential role in impacting the variable clinical outcome modulated by FoxO proteins. Only through the initiation and progression of future investigations can these questions be addressed to both safely and effectively develop FoxO signal transduction pathways into viable clinical treatments for metabolic disorders and DM.

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Table 1
FoxO Transcription Factors and Diabetes Mellitus

FoxO Proteins	Biology
Expression and Structure	FoxO proteins possess a butterfly-like appearance on X-ray crystallography and nuclear magnetic resonance
	FoxO proteins are present throughout the body and have a conserved forkhead domain described as a "winged helix"
Post -Translational Modification	FoxO proteins are modified by phosphorylation, acetylation, and ubiquitylation through pathways involving Akt, SgK, SIRT1, and Wnt signaling with WISP1
	Akt and SgK phosphorylate FoxO proteins at different sites affording various pathways to control FoxO protein activity
Programmed Cell Death	Under some conditions, the activation of FoxO proteins may prevent apoptotic cellular injury during oxidative stress
	FoxO protein activation can lead to the induction of autophagy and increase cell survival, such as during the clearance of toxic mHtt protein in neurons and during starvation to maintain cardiac function
	However, activation of FoxO proteins usually leads to apoptotic membrane PS externalization and DNA degradation. In some circumstances, a reduction in autophagy is required to block oxidative stress injury
Cellular Signaling	Wnt signaling can promote cellular protection against apoptotic cell death through the inactivation of FoxO proteins
	WISP1 can limit FoxO3a activity, block caspase 1 and 3 activity, and promote SIRT1 nuclear trafficking
	FoxO proteins can control SIRT1 transcription and increase SIRT1 expression. In addition, SIRT1 promotes FoxO-driven SIRT1 autotranscription through the activation and deacetylation of FoxO proteins
	Agents that are protective during DM, such as EPO and nicotinamide, can phosphorylate and inactive FoxO proteins to lead to cellular protection
Outcomes with Diabetes Mellitus	Some clinical studies suggest a detrimental effect associated with FoxO proteins and DM
	Inactivation of FoxO proteins during DM may protect pancreatic β-cells, retinal cells, renal cells, and glucose homeostasis
	In some clinical populations, FoxO protein activation may be protective during metabolic disorders for the immune system, assist with insulin signaling, and maintain energy reserves

Akt: protein kinase B; DM: diabetes mellitus; DNA: deoxyribonucleic acid; EPO: erythropoietin; FoxO: mammalian forkhead transcription factors of the O class; mHtt: mutant Huntingtin; PS: phosphatidylserine; SgK: serum- and glucocorticoid-inducible protein kinase; SIRT1: silent mating type information regulation 2 homolog 1 (*S. cerevisiae*); WISP1: wnt1 inducible signaling pathway protein 1; Wnt: proteins derived from the *Drosophila Wingless* (*Wg*) and the mouse *Int-1* genes