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Diabetes Mellitus: Channeling Care through Cellular Discovery

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Abstract

Diabetes mellitus (DM) impacts a significant portion of the world's population and care for this disorder places an economic burden on the gross domestic product for any particular country. Furthermore, both Type 1 and Type 2 DM are becoming increasingly prevalent and there is increased incidence of impaired glucose tolerance in the young. The complications of DM are protean and can involve multiple systems throughout the body that are susceptible to the detrimental effects of oxidative stress and apoptotic cell injury. For these reasons, innovative strategies are necessary for the implementation of new treatments for DM that are generated through the further understanding of cellular pathways that govern the pathological consequences of DM. In particular, both the precursor for the coenzyme β -nicotinamide adenine dinucleotide (NAD^+), nicotinamide, and the growth factor erythropoietin offer novel platforms for drug discovery that involve cellular metabolic homeostasis and inflammatory cell control. Interestingly, these agents and their tightly associated pathways that consist of cell cycle regulation, protein kinase B, forkhead transcription factors, and Wnt signaling also function in a broader sense as biomarkers for disease onset and progression.

Keywords

Aging; biomarkers; diabetes; erythropoietin; FoxO3a; oxidative stress; sirtuins; Wnt

DIABETES MELLITUS, ECONOMIC BURDEN, AND MULTI-SYSTEM COMPLICATIONS

Diabetes mellitus (DM) is a metabolic disorder closely associated with increased weight gain [1,2] and affects almost 20 million individuals in the United States and more than 165 million individuals worldwide [3]. By 2030, DM may be a condition to contend with in more than 360 million individuals. Furthermore, a significant portion of the population has undiagnosed diabetes, illustrating the need for improved early diagnosis [4]. Type 1 insulin-dependent DM

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is present in 5–10 percent of all diabetics, but is increasing in adolescent minority groups [1, 5]. Type 1 DM also leads to long-term complications throughout the body involving cardiovascular, renal, and nervous system disease [6]. Type 2 DM represents at least 80 percent of all diabetics, usually in individuals over 40 years of age, and is dramatically increasing in incidence as a result of changes in human behavior and increased body mass index [1,5]. Type 2 DM is characterized by a progressive deterioration of glucose tolerance with early β -cell compensation for insulin resistance (achieved by β -cell hyperplasia). This is subsequently followed by progressive decrease in β -cells mass. In addition, the growing incidence of impaired glucose tolerance in the young also is worrisome [7].

These statistics bring to light the emerging burden DM presents to the world healthcare system. Compared with other nations, the United States devotes 16% of the gross domestic product to healthcare. In addition, spending for each individual is the highest level in the world and is equal to \$7,290 [8]. Total spending on pharmaceuticals is also the highest in the world with \$878 per individual. However, life expectancy in years in the United States equals 78.1 years and trails behind other developed countries such as Japan (life expectancy of 82.6 years). The United States also is ranked as having the highest level of obesity in the population at 34.3% while countries such as Japan have a 3.4% level of obesity [8]. Patients with DM can develop a number of disorders that include immune dysfunction [9], sarcopenia [10], depression [11], hepatic dysfunction [12], renal disease [13], anemia and hematological disease [14–16], neurodegenerative disorders [5,17,18], and cardiovascular disease [5,19]. Interestingly, patients with DM are at risk for the development of cognitive disorders that may be associated with vascular disease [9,20]. In relation to neurodegenerative disease, DM may be associated with the development of Alzheimer's disease [21,22]. Alzheimer's disease can be the result of a number of etiologies [23,24], such as changes in cerebral blood flow and metabolism with aging [25], sialylation and glycosylation of amyloid plaques [26,27], aberrant cell cycle induction [28–30], amyloid toxicity [30–34], chemokine induction [35], exogenous toxins [36], alteration in muscarinic and nicotinic pathways [25,37], and intracellular calcium changes [38]. Additional studies for cognitive loss point to metabolic dysfunction [21,39,40]. For example, in animal models with brain/neuronal insulin receptor knockouts, loss of insulin signaling appears to be linked to increased phosphorylation of the microtubule-associated protein tau that occurs during Alzheimer's disease [41]. In clinical investigations, some studies report that diabetic patients may have significantly less neuritic plaques and neurofibrillary tangles than non-diabetic patients [42], but other investigators report a modest adjusted relative risk of Alzheimer's disease in patients with diabetes as compared with those without diabetes to be 1.3 [43]. Additional studies have described the reduced expression of genes encoding insulin in Alzheimer's patients that suggests a potential link between DM and the development of Alzheimer's disease [44].

DIABETES MELLITUS, OXIDANT PATHWAYS, AND INFLAMMATORY CELLS

These complications of DM are the result of multiple factors, but argue for the implementation of novel drug development strategies that are generated through the further understanding of cellular pathways that govern the pathological consequences of DM. In particular, cellular pathways that lead to DM and its complications have been tied to oxidant stress [1,2,17,18, 21,45,46]. In studies with Type 1 diabetic animals, oxidative stress leads to DNA damage in renal cortical cells [47]. Although early effects of elevated glucose may increase the presence of potentially protective pathways [48], more prolonged exposure of elevated glucose [15, 49] as was as the rise in insulin levels [50] can lead to reactive oxygen species (ROS) and can be detrimental even if glucose levels are controlled [51]. In addition, elevated levels of ceruloplasmin during hyperglycemia are suggestive of increased ROS [52]. A number of treatment entities seek to ameliorate the effects of oxidative stress during DM [34,53–56].

Oxidative stress also may promote the onset of DM by decreasing insulin sensitivity and destroying the insulin-producing cells. ROS can penetrate through cell membranes and cause damage to β -cells of pancreas [57,58]. A high fat diet [59] or free fatty acids also have been shown to release ROS and contribute to mitochondrial DNA damage and impaired pancreatic β -cell function [60]. In non-diabetic rats, hyperglycemia has been shown to increase muscle protein carbonyl content and elevated levels of malondialdehyde and 4-hydroxynonenal, indicators of oxidative stress and lipid peroxidation [61]. These biomarkers of oxidative stress and insulin resistance suggest that ROS contribute to the pathogenesis of hyperglycemia-induced insulin resistance [62,63]. Hyperglycemia can lead to increased production of ROS in several cell types, such as pancreatic beta-cells and vascular cells [63,64]. Chronic hyperglycemia is not necessary to lead to oxidative stress injury, since even short periods of hyperglycemia, generate ROS, such as in vascular cells [65]. Recent clinical correlates support these experimental studies to show that acute glucose swings in addition to chronic hyperglycemia can trigger oxidative stress mechanisms during Type 2 DM, demonstrating the importance for therapeutic interventions during acute and sustained hyperglycemic episodes [66].

At the cellular level, ROS are oxygen free radicals and other chemical entities that may lead to cell injury [28,67,68], but also have been tied to pain sensitivity [69]. Oxidative stress can result in hepatic injury [70,71], pancreatitis [72], impaired cognition and psychiatric disorders [22,73,74], neuronal injury [23,28,75–79], Parkinson's disease [80–83], complications of epilepsy [84], cardiovascular disease [85–87], ocular disease [88], age-related disorders [89], metal ion injury [90], and promote xenobiotic toxicity [91,92]. ROS consist of superoxide free radicals, hydrogen peroxide, singlet oxygen, nitric oxide (NO), and peroxynitrite [17,23,64]. ROS usually occur at low levels during normal physiological conditions and are scavenged by endogenous antioxidant systems that include superoxide dismutase (SOD), glutathione peroxidase, catalase, and vitamin D₃ [93,94]. Additional pathways include vitamins C, E, and K [84,95–98].

Oxidative stress leads to both apoptotic and non-apoptotic pathways. Apoptosis can occur during DM [1,2,99,100], anesthetic exposure [101], tissue ischemia [102–105], bone fatigue [106], neurodegenerative disorders [17,107–109] and Alzheimer's disease [30–33,38,110–115], plasticity associated with ischemic preconditioning [116], aging-related diseases [18, 117,118], and toxic conditions during development [101,119]. During apoptosis, the cleavage of genomic DNA into fragments [108,120,121] usually occurs after the exposure of membrane phosphatidylserine (PS) residues [122–127]. Membrane PS exposure occurs in neurons, vascular cells, and inflammatory microglia during reduced oxygen exposure [29,68,120,128, 129], β -amyloid (A β) exposure [32,34], nitric oxide exposure [130–134], and during the administration of agents that induce the production of reactive oxygen species (ROS), such as 6-hydroxydopamine [83]. Membrane PS externalization also occurs on platelets and has been associated with clot formation in the vascular system [135].

The activation of inflammatory cells such as microglia that can dispose of injured cells is also dependent upon membrane PS externalization [136,137]. For their own survival, microglia and non-neuronal cells of the brain are dependent upon several intracellular pathways, such as mTOR [138,139] and zinc regulation [140]. Non-neuronal cells of the brain can be beneficial to modulate neurogenesis [141], to function as immune surveillance for toxic products [142], such as for β -amyloid [27], to block foreign organisms and viral agents from proliferating in the brain [143], to modulate vascular growth [144], and to allow for the repair of tissues composed of neuronal and vascular cells [138,145]. However, microglia once stimulated also can promote cell injury and death. Microglia generate ROS [146,147] that can worsen events with oxidative stress injury [148] and activate cytokines that in some circumstances may initially lead to cell proliferation [149], but later can result in the demise of cells [35,143,

144]. For these reasons, it is important to understand the mechanisms that can activate microglia. Membrane PS exposure can become a signal for microglia to dispose of injured cells [40,122,125,126,150]. This process can be controlled by caspase 1 and caspase 3 [68,151,152]. Increased expression of the phosphatidylserine receptor (PSR) on microglia also occurs to facilitate activation of microglia [32,56,152,153].

DIABETES MELLITUS, ENERGY MAINTENANCE, AND NICOTINAMIDE

Cellular pathways in DM are closely associated to cellular energy maintenance and intact mitochondrial function [5,9,45,154–156]. Oxidant stress and ROS exposure can result in the opening of the mitochondrial membrane permeability transition pore [125,157–159], reduce mitochondrial NAD⁺ stores [21], and result in apoptotic cell injury [23]. Free fatty acids also can lead to ROS release, mitochondrial DNA damage, and impaired pancreatic β -cell function [60]. In DM, mitochondrial dysfunction also has been described. In patients with Type 2 DM, skeletal muscle mitochondria have been observed to be smaller than those in control subjects [160]. The development of Type 2 DM has been associated with a decrease in the levels of mitochondrial proteins and mitochondrial DNA [161].

One agent, namely nicotinamide, and the cellular pathways that it modulates may be critical for the maintenance of cellular energy homeostasis. Nicotinamide, the amide form of vitamin B₃ (niacin) and nicotinamide or nicotinic acid is the water soluble form vitamin B₃, is the principal form of niacin in dietary plant sources is nicotinic acid that is rapidly absorbed through the gastrointestinal epithelium [162]. Nicotinamide is subsequently generated through the conversion of nicotinic acid in the liver or through the hydrolysis of NAD⁺ [21]. Once nicotinamide is absorbed, it functions as the precursor for the coenzyme β -nicotinamide adenine dinucleotide (NAD⁺) [40,163] and also is essential for the synthesis of nicotinamide adenine dinucleotide phosphate (NADP⁺) [164]. Nicotinamide is changed to its mononucleotide form (NMN) with the enzyme nicotinic acid/nicotinamide adenyltransferase yielding the dinucleotides NAAD⁺ and NAD⁺. NAAD⁺ also yields NAD⁺ through NAD⁺ synthase [165] or NAD⁺ can be synthesized through nicotinamide riboside kinase that phosphorylates nicotinamide riboside to NMN [166,167]. Nicotinamide through NAD⁺ is vital in cellular metabolism and can be directly utilized by cells to synthesize NAD⁺ [17,40,95]. Nicotinamide also participates in energy metabolism through the tricarboxylic acid cycle by utilizing NAD⁺ in the mitochondrial respiratory electron transport chain for the production of ATP, DNA synthesis, and DNA repair [168–170].

During a number of conditions, nicotinamide is important for cell development and protection. Nicotinamide can be essential for the differentiation of human embryonic stem cells [171]. Nicotinamide also has more protean endocrine effects [172,173] and offers protection for both neuronal [174–176] and vascular cells [17,40,95,163]. In neuronal cell populations, nicotinamide protects against free radical injury [159], anoxia [177], excitotoxicity [178], homocysteine toxicity [179], ethanol-induced neuronal injury [180], and oxygen-glucose deprivation [175,181]. In cortical neurons, nicotinamide blocks cell injury during ROS generating toxins such as tertiary butylhydroperoxide [182]. Nicotinamide also can protect both rod and cone photoreceptor cells against N-methyl-N-nitrosourea toxicity [183,184] as well as against glycation end products in all layers of the retina [185]. In animal studies, nicotinamide improves cognitive function, cell survival, and reduces edema following cortical trauma [186–191], limits axonal degeneration [192], reduces cerebral ischemia [193–195] sometimes more effectively in models that were absent of comorbidities [196], prevents spinal cord injury [197,198], and lessens disability in models of Parkinson's disease [80,199,200]. In vascular cells [174–176], nicotinamide supports endothelial cell survival [40,95,163] especially during ROS exposure [159,177,201,202] which may be crucial for tissue growth and repair [203]. Nicotinamide can protect the function of the blood brain barrier [186,187],

influence arteriolar dilatation and blood flow [204], increase skin vascular permeability [205], inhibit atherosclerotic plaque formation through inhibition of poly(ADP-ribose) polymerase [206], and foster platelet production through megakaryocyte maturation [207].

Interestingly, nicotinamide also may reverse a previously sustained early apoptotic injury [40,159,175,177,201,208], suggesting that apoptosis prior to reaching genomic DNA degradation is dynamic and reversible in nature [40,159,177,209]. Yet, some studies suggest that nicotinamide may either prevent or contribute to atherosclerotic plaques over a three to six month progression [210]. Although the mechanisms are not clear for the promotion of atherosclerosis, it is conceivable that these events may occur during oxidative stress and the production of acidosis-induced cellular toxicity [211–213], since nicotinamide cannot prevent cellular injury during intracellular acidification paradigms [159].

More importantly, nicotinamide plays a significant role during DM. Nicotinamide has been suggested to have a close relationship with metabolic pathways that may lead to clinical cognitive changes [214]. Nicotinamide can maintain normal fasting blood glucose with streptozotocin-induced DM in animal models [215,216], limit peripheral nerve injury during elevated glucose [217], reverse Type 1 DM in mice with acetyl-L-carnitine [218], and block oxidative stress [180,201,208,219,220]. Nicotinamide also affects levels of O-N-acetylglucosamin(O-GlcNAc)ylated proteins [221] and can significantly improve glucose utilization, prevent excessive lactate production in ischemic animal models [222]. In patients, nicotinamide (1200 mg/m²/day) protects β -cell function and prevents clinical disease in islet-cell antibody-positive first-degree relatives of Type 1 DM [223]. Nicotinamide also can reduce HbA_{1c} levels in patients with recent onset Type 1 DM combined with intensive insulin therapy for up to two years after diagnosis [224]. Also relevant to patients with DM and renal insufficiency, nicotinamide can reduce intestinal absorption of phosphate and prevent the development of hyperphosphatemia [225]. Yet, some caution must be exercised with nicotinamide. Investigations have reported that elevated nicotinamide levels actually may foster DM [226] and that prolonged exposure to nicotinamide may lead to impaired β -cell function and reduction in cell growth [227,228]. Furthermore, nicotinamide also may inhibit P450 and hepatic metabolism [229] and play a role in the progression of other disorders such as Parkinson's disease [200].

There are several pathways that nicotinamide may use to maintain cellular metabolic homeostasis [18,21,40,95,171] and provide protection for cells during DM [159,201]. Nicotinamide can function at the level of mitochondrial membrane pore formation [40,201,209] to prevent the release of cytochrome c [208] that may involve the phosphorylation of Bad [208]. Nicotinamide also can prevent mitochondrial membrane depolarization during exposure to either *tert*-butylhydroperoxide or atractyloside [175] and may inhibit the assembly of the mitochondrial permeability transition pore complex similar to the action of cyclosporin A [230] as well as stabilize cellular energy metabolism through ATP pathways [231]. Nicotinamide also blocks forkhead transcription factor activity, such as FoxO3a, through phosphorylation [175,232], and may be protective through mechanisms of post-translational modification of FoxO3a and inhibition of caspase 3 activity [18,137,233–235].

Nicotinamide also is closely linked to cell longevity pathways that involve sirtuins [95,236,237]. These include the sirtuin Sirt1, a NAD⁺-dependent deacetylase and the mammalian ortholog of the silent information regulator 2 (Sir2) protein [238], that can control multiple processes such as cell injury, lifespan, and metabolism [239,240]. Sirtuins have been associated with cell longevity and aging as shown by early studies linking DAF-16 in *Caenorhabditis elegans* [137,238,240–242]. Furthermore, sirtuins are tied to cellular metabolism [239,243] and increased cell survival [240,241,244–246]. However, the relationship between nicotinamide and sirtuins is not entirely clear, but sirtuin activation may promote glucose

homeostasis and insulin sensitivity [21,239,240,246,247] while also reducing the risk of obesity [248]. In regards to nicotinamide, this agent prevents oxidative stress-induced apoptotic injury usually in a specific concentration range. Administration of nicotinamide in a range of 5.0–25.0 mmol/L significantly protects cells during oxidative stress injuries. This concentration range is similar to other injury paradigms in both animal models [184] and in cell culture models [40,159,201]. In contrast to these cytoprotective concentrations of nicotinamide that also can modulate gene regulation [249], a reduction in nicotinamide levels during nicotinamidase expression supports increased cellular survival and longevity [244, 246]. Nicotinamide can block cellular Sir2 by intercepting an ADP-ribosyl-enzyme-acetyl peptide intermediate with the regeneration of NAD⁺ (transglycosidation) [250]. Physiological concentrations of nicotinamide noncompetitively inhibit Sir2, promoting the premise that nicotinamide is a physiologically relevant regulator of Sir2 enzymes [251]. Yet, nicotinamidase expression, which reduces nicotinamide concentrations, prevents both apoptotic late DNA degradation and early PS exposure that appears to depend upon increased Sirt1 activity and may serve to modulate inflammatory cell activation [244,246]. In addition, inhibition of sirtuin (Sirt1) activity either by pharmacological methods or siRNA gene silencing is detrimental to cell survival during oxidative stress and blocks nicotinamidase protection, further supporting that Sirt1 activity may be necessary for nicotinamidase protection during oxidative stress. As a result, it is the lower concentrations of nicotinamide that can function as an inhibitor of sirtuins that are necessary for the promotion of increased lifespan and cellular survival [175,177,201, 208,244,246,252], at least in yeast and metazoans [95,236,237]. Furthermore, sirtuin activity also may prevent nicotinamide from assisting with DNA repair by altering the accessibility of DNA damaged sites for repair enzymes [253].

DIABETES MELLITUS, ERYTHROPOIETIN, AKT, FORKHEAD, AND WNT

Erythropoietin (EPO) is approved by the Food and Drug Administration for the treatment of anemia [63,64]. Yet, enthusiasm for the use of this agent throughout the body has grown considerably since a growing number of investigations have identified EPO as an agent with effective utility for multiple disease processes [254,255]. Treatment considerations include therapy for depression [256], Alzheimer's disease [31,257,258], Parkinson's disease [259], immune system dysfunction [130,260–263], neurodegeneration [31,53,130,260,264–267], cardiovascular disorders [158,261,268–276], spinal cord injury [277,278], brain edema [279], fertility [280], trauma [281–283], shock [284–286], infection [287–289], pulmonary disease [290–292], renal disease [49,293–295], gastrointestinal disorders [296–298], retinal disease and glaucoma [299–302], and metabolic disorders [1,16,17,53,54,303].

EPO is present in the brain, heart, and vascular system [260,261,270,304–306] as well as being required for erythropoiesis [307–309]. EPO production occurs throughout the body [64,255, 310] and can be detected in the breath of healthy individuals [311]. The principal organs of EPO production and secretion are the kidney, liver, brain, and uterus [232,312,313].

In patients with DM, plasma EPO is often low in individuals with anemia [314] or without anemia [315]. The inability of these individuals to produce EPO in response to declining hemoglobin levels may indicate an impaired EPO response during DM [316]. Yet, increased EPO secretion during diabetic pregnancies may represent the body's attempt at endogenous protection against the complications of DM [317,318]. EPO in diabetic as well as non-diabetic patients with severe, resistant congestive heart failure can decrease fatigue, increase left ventricular ejection fraction, and significantly decrease hospitalization stay [319]. In addition, EPO can serve to reverse the complications of anemia during DM [16]. The potential cytoprotective capacity of EPO may be important during other complications of DM, such as those that involve cognitive and neuronal synaptic impairment. Elevated EPO concentrations during infant maturation have been correlated with increased Mental Development Index

scores [320] and EPO may prevent toxic effects of agents used to control cognitive function such as haloperidol [321]. In animal models, EPO may reduce apoptotic pathways during periods of hyperoxia in the developing brain [322,323]. Furthermore, some clinical disorders may present with periods of hyperoxia followed by combined cerebral hypoperfusion and hypoxia that can lead to cerebral injury with associated oxidative stress [324]. EPO under these conditions may be protective since it can promote neurite outgrowth [325] and also may regulate hemoglobin levels that have recently been associated with cognitive decline [326]. Experimental work during elevated glucose also has demonstrated that EPO can significantly improve vascular cell survival in a 1.0 ng/ml range [54]. EPO administration in patients also can significantly increase plasma levels of EPO well above this range of 1.0 ng/ml that has been associated with potential EPO cellular protection in patients with cardiac or renal disease [327,328], illustrating that the effects of EPO observed during *in vitro* studies may parallel the cellular processes altered by EPO in patients with DM [320].

Cellular protection by EPO is dependent upon multiple pathways, but three pathways in particular offer exciting perspectives for the future applications of EPO in clinical disease and especially during DM. One novel pathway involves protein kinase B (Akt). Activation of Akt can foster cell survival, such as during cell proliferation [329], progenitor cell development [149], blood-brain barrier permeability [330], inflammation [143,331], ischemic-preconditioning [332], neurodegeneration [83], hyperglycemia [48,333], hypoxia [270], amyloid toxicity [31,32,110,111,334], excitotoxicity [75], amyloid production [335], cardiomyopathy [336], cellular aging [337], and oxidative stress [125,126,338]. Akt activation also can modulate microglial cell activation [125,126,158], regulate transcription factors [261], maintain mitochondrial membrane potential ($\Delta\Psi_m$), prevent cytochrome c release [130,158,260], and block caspase activity [158,260,270]. The benefits of Akt to foster cell survival should be noted as potentially detrimental during tumor growth and during cancer resistance to chemotherapy [339].

EPO administration leads to the activation of Akt and protects against genomic DNA degradation and membrane PS exposure [130,152,260,261,270,306,340–345]. Up-regulation of Akt activity, such as during vascular and cardiomyocyte ischemia [341,342], free radical exposure [260,346], matrix detachment [347], neuronal axotomy [348], N-methyl-D-aspartate toxicity [349], hypoxia [270,350], β -amyloid toxicity [31,351], DNA damage [126,270,338, 352], metabotropic receptor signaling [76,85,151,353], cell metabolic pathways [40,208], cytochrome c release [130,270,341], caspase activity [158,260,270], and oxidative stress [125,126,338] increases cell survival. Akt also can directly control microglial activation through the prevention of Bcl-x_L degradation [338] and the inhibition of caspase 1-, 3-, and 9-like activities [125,126,151].

Akt also functions as a primary regulatory element for FoxOs, the forkhead transcription factors of the “O” class [238,354]. These transcription factors bind to DNA through the forkhead domain that relies upon fourteen protein-DNA contacts [234,354–357]. The original nomenclature for these proteins, such as forkhead in rhabdomyosarcoma (*FKHR*), the *Drosophila* gene fork head (*fkh*), and Forkhead RElated ACTivator (FREAC)-1 and -2, has been replaced [233]. The present nomenclature for human Fox proteins places all letters in uppercase, otherwise only the initial letter is listed as uppercase for the mouse, and for all other chordates the initial and subclass letters are in uppercase [358]. Members of this family that include FoxO1, FoxO3, FoxO4, and FoxO6 are found throughout the body [63,233,235]. These proteins are expressed in tissues of the reproductive system of males and females, skeletal muscle, the cardiovascular system, lung, liver, pancreas, spleen, thymus, and the nervous system [137,234,357,359]. Modulation of FoxOs is a viable therapeutic target for systems that involve metabotropic glutamate receptors [76], neurotrophins [360], cancer [137,357,361], and cytokines [261] to foster intended cell survival.

EPO modulates FoxOs for both cellular development and survival. EPO fosters erythroid progenitor cell development through the regulation of FoxO activity [255,310,362] and may require regulation of specific gene expression through an EPO-FoxO3a association to promote erythropoiesis in cultured cells [363]. In addition, EPO controls the phosphorylation and degradation of FoxO3a to retain it in the cytoplasm by binding to 14-3-3 protein and leads to increased cellular survival during oxidative stress [261]. Without the presence of EPO during oxidative stress injuries, FoxO3a is able to translocate from the cytoplasm of cells to the nucleus to initiate a “pro-apoptotic” program (Fig. 1).

Yet, FoxO proteins are involved in a number of other cellular pathways that are also closely tied to DM. For example, FoxOs control cell cycle progression to prevent tumor growth [137,357,364]. Since attempted initiation of the cell cycle such as in neurons may be detrimental and can lead to cell death [28,29,365,366], one may consider the ability of FoxO proteins to block cell cycle progression to be beneficial in these circumstances. In regards to DM, FoxO proteins may be cytoprotective. Interferon-gamma driven expression of tryptophan catabolism by cytotoxic T lymphocyte antigen 4 may activate Foxo3a to protect dendritic cells from injury in nonobese diabetic mice [367]. In addition, adipose tissue-specific expression of Foxo1 in mice improves glucose tolerance and sensitivity to insulin during an elevated fat diet [368]. FoxO proteins also may protect against diminished mitochondrial energy levels known to occur during insulin resistance such as in the elderly populations [1,2,5]. In caloric restricted mice that have decreased energy reserves, Foxo1, Foxo3a, and Foxo4 mRNA levels were noted to progressively increase over two years [369]. These observations complement studies in *Drosophila* and mammalian cells that demonstrate an increase in insulin signaling to regulate cellular metabolism during the up-regulation of FoxO1 expression [370].

It should be noted that the role of FoxO proteins in different cell systems can be variable and does not always point to a beneficial effect of FoxO proteins. FoxO3a controls early activation and subsequent apoptotic injury in microglia through caspase action of caspase 3, 8, and 9 [34,56], illustrating that targeting FoxO3a activity may limit apoptotic caspase activity and promote cell survival. Analysis of the genetic variance in *FOXO1a* and *FOXO3a* on metabolic profiles, age-related diseases, fertility, fecundity, and mortality in patients have shown higher HbA_{1c} levels and increased mortality risk associated with specific haplotypes of *FOXO1a* [371]. These clinical observations may indicate that elevated glucose levels can reduce post-translational phosphorylation of FOXO1, FOXO3a, and FOXO4 and initiate cellular apoptosis [372]. In addition, mice with a constitutively active Foxo1 transgene have increased microsomal triglyceride transfer protein and high plasma triglyceride levels [373]. Increased transcriptional activity of FoxO1, such as by the Sirt1 activator resveratrol, also can decrease insulin mediated glucose uptake and result in insulin resistance [374]. Overexpression of Foxo1 in skeletal muscles of mice can lead to a reduction in skeletal muscle mass and poor glycemic control [375]. Other studies that block the expression of Foxo1 in normal and cachectic mice [376] or reduce FoxO3 expression [377] demonstrate positive effects with an increase in skeletal muscle mass or resistance to muscle atrophy.

EPO also is intimately involved with a third pathway, namely those cell pathways controlled by Wnt signaling [17,254,378]. Wnt proteins derived from the *Drosophila Wingless (Wg)* and the mouse *Int-1* genes are secreted cysteine-rich glycosylated proteins that play a role in a variety of cellular functions [32,54,153,379]. Wnt proteins are involved in embryonic cell proliferation, cell differentiation, and cell survival that involve neurons, cardiomyocytes, endothelial cells, red blood cells, tumors, adipose tissue as well as several other cell types [235,378,380–391].

In relation to metabolic conditions, abnormalities in Wnt pathways that involve transcription factor 7-like 2 gene may impart increased risk for type 2 DM in some populations [392–394]

and have a strong association with the development of obesity [395]. The family member Wnt5b also has been shown to have an elevated expression in adipose tissue, the pancreas, and the liver in patients with DM, suggesting control of metabolic pathways by Wnt [396]. Experimental animal studies with hyperglycemia following a high fat diet also show increased expression of Wnt3a and Wnt7a [397]. Intact Wnt family members may offer glucose tolerance and increased insulin sensitivity [398] as well as protect against DM complications such as renal glomerular mesangial cells injury [399]. In addition, animals that over express Wnt10b with a high-fat diet experienced a reduction in bodyweight, hyperinsulinemia, triglyceride plasma levels, and improved glucose homeostasis [400]. In contrast, patients with impaired Wnt signaling through a missense mutation in LRP-6 can have associated conditions with coronary artery disease and the combined metabolic syndrome with hypertension, hyperlipidemia, and DM [401]. This potential protective capacity of Wnt appears to extend to EPO [54,254,313]. Wnt1 protein is necessary and sufficient to promote cellular protection during elevated glucose exposure [54]. Administration of exogenous Wnt1 protein can significantly prevent apoptotic vascular cell injury during elevated glucose exposure. EPO also maintains the expression of Wnt1 during elevated glucose exposure and prevents loss of Wnt1 expression that would occur in the absence of EPO during elevated glucose. Blockade of Wnt1 with a Wnt1Ab can neutralize the protective capacity of EPO, demonstrating that Wnt1 is a critical component in the protective capacity of EPO during elevated glucose exposure [54].

FUTURE CONSIDERATIONS

Innovative investigations into the pathways that determine the dysfunction and injury of cellular systems during DM can lead the way for the development of new therapeutic inroads. In particular, both nicotinamide and EPO in conjunction with the signal transductions that are controlled by these agents offer novel platforms for drug discovery. Yet, these agents and their associated pathways also function in a broader sense as biomarkers for disease onset and progression. Biomarkers can involve the use of specific genes, proteins, or products of cellular and biological processes and may represent the response of cells or tissues to therapeutic strategies [62]. For example, loss of FoxO tissue expression may be a gauge for tumor progression [402] while enhanced FoxO protein expression may suggest an effective response to chemotherapy [361,403,404]. To a similar degree, the cellular expression of EPO and its receptor during injury paradigms also may indicate an effective treatment response [264,290, 313], but during neoplastic growth may alternatively suggest a poor prognosis [405]. In regards to Wnt, the presence of this protein may be indicative of early tissue injury during elevated glucose [54], amyloid toxicity [32], or cardiac ischemia [406,407]. Yet, the aberrant expression of Wnt under different circumstances may signal progressive prostate cancer and bone metastases [408], the induction of cancer stem cells [380], or the vulnerability of patients with Type 2 DM to develop colorectal tumors [409]. Future investigations into these pathways and the complexities that they hold will continue to channel clinical care into effective and innocuous strategies for both the prevention and treatment of DM.

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Fig. (1). Subcellular trafficking of FoxO3a occurs during oxidative stress to allow for “pro-apoptotic” transcription

Inflammatory microglial cells were imaged with immunofluorescent staining for **FoxO3a** (Texas-red streptavidin) six hours following oxidative stress exposure with oxygen-glucose deprivation (**OGD**). Nuclei of microglia were counterstained with **DAPI**. In merged images, untreated control microglia have readily visible nuclei (white/blue in color) that illustrate absence of **FoxO3a** in the nucleus. In contrast, merged images after **OGD** exposure show diffusely red cytoplasm and nucleus with minimal visibility of the nucleus with **DAPI** illustrating translocation of **FoxO3a** to the nucleus.