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NOVEL AVENUES OF DRUG DISCOVERY AND BIOMARKERS FOR DIABETES MELLITUS

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Abstract

Globally, developed nations spend a significant amount of their resources on healthcare initiatives that poorly translate into increased population life expectancy. As an example, the United States devotes sixteen percent of its gross domestic product to healthcare, the highest level in the world, but falls behind other nations that enjoy greater individual life expectancy. These observations point to the need for pioneering avenues of drug discovery to increase lifespan with controlled costs. In particular, innovative drug development for metabolic disorders such as diabetes mellitus (DM) becomes increasingly critical given that the number of diabetic individuals will increase exponentially over the next twenty years. Here we discuss the elucidation and targeting of novel cellular pathways that are intimately tied to oxidative stress in DM for new treatment strategies. Pathways that involve wingless, NAD^+ precursors, and cytokines govern complex biological pathways that determine both cell survival and longevity during DM and its complications. Furthermore, the role of these entities as biomarkers for disease can further enhance their utility irrespective of their treatment potential. Greater understanding of the intricacies of these unique cellular mechanisms will shape future drug discovery for DM to provide focused clinical care with limited or absent long-term complications.

Keywords

biomarkers; diabetes; oxidative stress

Healthcare and metabolic disease

Compared with other nations throughout the world, the United States devotes 16% of the gross domestic product to healthcare and spending for each individual equal to $7,290, the

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highest levels in the world [1]. Total spending on pharmaceuticals is also the highest in the world with $878 per individual. Yet, life expectancy in years in the United States equals 78.1 years and trails behind other countries such as Japan that allots 8% of the gross domestic product on healthcare, spends $2,514 for each individual, and has a life expectancy of 82.6 years. Furthermore, the United States 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 [1]. These statistics are the results of multiple factors, but also can support the arguments for not only improved preventive health measures, but also new directions to treat multiple disorders that can lead to improved lifespan while minimizing economic burden.

In particular, one can consider diabetes mellitus (DM), a metabolic disorder closely associated with increased weight gain [2, 3]. DM reaches approximately 20 million individuals in the United States and more than 165 million individuals worldwide [4]. By 2030, DM may affect more than 360 million individuals. Additionally, a significant portion of the population has undiagnosed diabetes, illustrating the need for improved early diagnosis [5]. The incidence of impaired glucose tolerance in the young also raises further concerns [6]. Individuals with impaired glucose tolerance have a greater than twice the risk for the development of diabetic complications than individuals with normal glucose tolerance [7].

Type 1 insulin-dependent DM is present in 5-10 percent of all diabetics, but is increasing in adolescent minority groups [2, 8]. Furthermore, Type 1 DM leads to long-term complications throughout the body involving cardiovascular, renal, and nervous system disease [9]. Type 1 DM is associated with the presence of alleles of the Human leukocyte antigen (HLA) class II genes within the major histocompatibility complex (MHC). The disorder is considered to have autoimmune origins resulting from inflammatory infiltration of the islets of Langerhans and the selective destruction of β-cells in the pancreas that leads to insulin loss [10]. In Type 1 DM, activation of T-cell clones that are capable of recognizing and destroying β-cells lead eventually to severe insulin deficiency. These T-cell clones are able to escape from thymus control that yield high affinity for major histocompatibility complex (MHC) molecules with T-cell receptors but incorrect low affinity for self-peptides. Once released into the bloodstream, these T-cell clones can become activated to destroy self-antigens. In many cases, the insulin gene (INS) and the human MHC or HLA complex are believed to contain the loci with *IDDM1* and *IDDM2* to account for the susceptibility to Type 1 DM with defective antigen presentation [11, 12]. Interestingly, a HLA class II molecule has been linked to Type 1 DM inheritance. HLA-DQ that lacks a charged aspartic acid (Asp-57) in the β-chain is believed to lead to the ineffective presentation of autoantigen peptides during thymus selection of T-cells [13]. Animal models that involve the nonobese diabetic (NOD) mice further support these findings, since these mice spontaneously develop diabetes with the human predisposing HLA-DQ corresponding molecule of H2 I-Ag. Yet, NOD mice without H2 I-Ag do not develop diabetes [14].

Upon initial diagnosis, approximately ninety percent of individuals with Type 1 DM have elevated titers of autoantibodies (Type 1A DM). The remaining ten percent of Type 1 DM individuals do not have serum autoantibodies and are described as having maturity-onset diabetes of the young (MODY) that can be a result of β-cell dysfunction with autosomal-dominant inheritance (Type 1B DM) [15]. Other variables reported in patients with Type 1 DM include the presence of insulin resistance that is usually characteristic of Type 2 DM and can lead to neurological and vascular disease [16, 17]. Interestingly, there is a converse overlap with Type 1 and Type 2 DM, since almost ten percent of Type 2 DM patients may have elevated serum autoantibodies [18].

Monogenic inheritance does not appear to lead to Type 1 DM. Prior work demonstrates that multiple loci with possible epistatic interactions among other loci may be responsible for

genetic transmission [19, 20]. In addition, several environmental factors may have a role with Type 1 DM such that investigations have suggested that Type 1 DM in monozygotic twins can occur with a cumulative risk of seventy percent from birth to 35 years of age [21, 22]. Other studies indicate a concordance between monozygotic twins to be approximately fifty percent [23], suggesting that environmental factors also may lead to a predisposition for Type 1 DM. Loss of autoimmunity in Type 1 DM can be precipitated also by the exposure to infectious agents [24].

Type 2 noninsulin-dependent 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 [2, 8]. 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 contrast, gestational diabetes mellitus that represents glucose intolerance during some cases of pregnancy usually subsides after delivery.

Insulin resistance or defective insulin action occurs when physiological levels of insulin produce a subnormal physiologic response. Skeletal muscle and liver are two of the primary insulin-responsive organs responsible for maintaining normal glucose homeostasis. Insulin lowers the level of blood glucose through suppression of hepatic glucose production and stimulation of peripheral glucose uptake, but metabolic disorders can result in insulin resistance and elevated serum glucose levels. Although insulin resistance forms the basis for the development of Type 2 DM, elevated serum glucose levels also are a result of the concurrent impairment in insulin secretion. This abnormal insulin secretion may be a result of defective β-cell function, chronic exposure to free fatty acids and hyperglycemia, and the loss of inhibitory feedback through plasma glucagon levels [25].

Patients with DM can develop multiple complications that include immune dysfunction [26], sarcopenia [27], depression [28], hepatic dysfunction [29], renal disease [30], anemia and hematological disease [31-33], neurodegenerative disorders [8, 34, 35], and cardiovascular disease [8, 36]. Interestingly, patients with DM are at risk for the development of cognitive disorders [26, 37]. In a prospective population based study of 6,370 elderly individuals, patients with DM had almost twice the risk for the development of dementia [38]. DM also has been found to increase the risk for vascular dementia in elderly subjects [39, 40]. Although some studies have found that diabetic patients may have significantly less neuritic plaques and neurofibrillary tangles than non-diabetic patients [41], 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 [42, 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 [43]. Alzheimer's disease can be the result of a number of etiologies [44, 45], such as changes in cerebral blood flow and metabolism with aging [46], sialylation and glycosylation of amyloid plaques [47, 48], aberrant cell cycle induction [49-51], amyloid toxicity [51-55], chemokine induction [56], exogenous toxins [57], alteration in muscarinic and nicotinic pathways [46, 58], and intracellular calcium changes [59]. Yet, other studies point to metabolic dysfunction [60-62]. 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 [63].

Oxidative stress, apoptotic injury, mitochondria, and diabetes

Many of the cellular pathways that lead to diabetic complications and insulin resistance have been linked to the generation of free radicals and oxidative stress [2, 3, 34, 35, 62, 64, 65]. In

animal studies with Type 1 diabetic animals, oxidative stress leads to DNA damage in renal cortical cells [66]. Although early effects of elevated glucose may increase the presence of potentially protective pathways [67], more prolonged exposure of elevated glucose can lead to reactive oxygen species (ROS) [32, 68] and can be detrimental even if glucose levels are controlled [69]. In addition, elevated levels of ceruloplasmin during hyperglycemia are suggestive of increased ROS [70]. A number of treatment entities seek to ameliorate the effects of oxidative stress during DM [55, 71-75].

Oxidative stress also may promote the onset of DM by decreasing insulin sensitivity and destroying the insulin-producing cells within the pancreas. For example, ROS can penetrate through cell membranes and cause damage to β-cells of pancreas [76, 77]. A high fat diet [78] or free fatty acids also have been shown to release ROS and contribute to mitochondrial DNA damage and impaired pancreatic β-cell function [79]. Interestingly 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 [80]. These biomarkers of oxidative stress and insulin resistance suggest that ROS contribute to the pathogenesis of hyperglycemia-induced insulin resistance [81, 82] as well as insulin induced ROS [73]. Hyperglycemia can lead to increased production of ROS in several cell types [82, 83]. For example, with increased age in a rat model of nonobese Type 2 DM, increased levels of 8-OHdG and HNE-modified proteins in pancreatic beta-cells have been reported [84]. Elevated glucose also has been shown to increase antioxidant enzyme levels in human endothelial cells, suggesting that elevated glucose levels may lead to a reparative process to protect cells from oxidative stress injury [85]. Chronic hyperglycemia is not necessary to lead to oxidative stress injury, since even short periods of hyperglycemia, generate ROS, such as in vascular cells [86]. 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 [87].

At the cellular level, ROS are oxygen free radicals and other chemical entities that can lead to cell injury if left unchecked [49, 88, 89]. Oxidative stress can result in hepatic injury [90, 91], pancreatitis [92], impaired cognition [93, 94], neuronal injury [44, 49, 95-99], Parkinson's disease [100-103], complications of epilepsy [104], cardiovascular disease [105-107], ocular disease [108], age-related disorders [109], metal ion injury [110], uncontrolled pain sensation [111], and promote xenobiotic toxicity [112, 113]. ROS consist of superoxide free radicals, hydrogen peroxide, singlet oxygen, nitric oxide (NO), and peroxynitrite [34, 44, 83]. 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 D_3 [114, 115]. Additional pathways include vitamins C, E, and K [104, 116-119].

Oxidative stress results in cell injury through apoptotic and non-apoptotic pathways. In regards to programmed cell death (apoptosis), apoptosis can occur during DM [2, 3, 120, 121], anesthetic exposure [122], tissue ischemia [123-126], bone fatigue [127], neurodegenerative disorders [34, 128-130] and Alzheimer's disease [51-54, 59, 131-136], plasticity associated with ischemic preconditioning [137], aging-related diseases [35, 138, 139], and toxic conditions during development [122, 140].

During apoptosis, the cleavage of genomic DNA into fragments occurs [129, 141, 142] as a later event during apoptotic injury [142-145] after the exposure of membrane phosphatidylserine (PS) residues [146, 147]. Membrane PS exposure occurs in neurons, vascular cells, and inflammatory microglia during reduced oxygen exposure [50, 89, 141, 148, 149], β-amyloid (Aβ) exposure [53, 55], nitric oxide exposure [150-154], and during the administration of agents that induce the production of reactive oxygen species (ROS), such as 6-hydroxydopamine [103]

(Figure 1). Membrane PS externalization also occurs on platelets and has been associated with clot formation in the vascular system [155].

Membrane PS exposure also is involved in the activation of inflammatory cells such as microglia of the central nervous system that can dispose of injured cells [156, 157]. For their own survival, microglia and non-neuronal cells of the brain are dependent upon several intracellular pathways, such as mTOR [158, 159] and zinc regulation [160]. Non-neuronal cells of the brain can be beneficial to modulate neurogenesis [161], to function as immune surveillance for toxic products [162], such as for β-amyloid [48], to block foreign organisms and viral agents from proliferating in the brain [163], to modulate vascular growth [164], and to allow for the repair of tissues composed of neuronal and vascular cells [158, 165]. Yet, microglia have another side that may be detrimental to an organism. They can generate ROS [166, 167], may worsen events with oxidative stress injury [168], and activate cytokines that in some circumstances may initially lead to cell proliferation [169], but later can result in the demise of cells [56, 163, 164]. 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 [61, 145, 170-172]. This process can be controlled by caspase 1 and caspase 3 [89, 173, 174]. Increased expression of the phosphatidylserine receptor (PSR) on microglia also occurs to facilitate activation of microglia [116, 175].

Oxidative stress and apoptotic cell death during disorders such as DM are also strongly associated to cellular energy maintenance and intact mitochondrial function [8, 26, 64, 176-178]. ROS exposure can result in the opening of the mitochondrial membrane permeability transition pore [145, 179-181], reduce mitochondrial NAD^+ stores, and result in apoptotic cell injury [44]. Free fatty acids also can lead to ROS release, mitochondrial DNA damage, and impaired pancreatic β-cell function [79]. In patients with Type 2 DM, skeletal muscle mitochondria have been described to be smaller than those in control subjects [182]. A decrease in the levels of mitochondrial proteins and mitochondrial DNA in adipocytes also has been correlated with the development of type 2 DM [183].

Innovative drug discovery for DM

Multiple pathways may lead to a loss in cell survival and longevity during DM that are broad in nature and consist of several precipitating factors. Yet, oxidant-induced injury and the cellular pathways responsible for this signaling are thought to be primary mediators of the disability that ensues during DM. As a result, novel and pioneering directions for drug discovery are required for safe and effective treatments for DM. In addition, it is the understanding of the complex nature of cellular pathways and their intimate relationship that is critical for the development of successful drug platforms. Here we present novel cellular pathways that are strongly bound to oxidant pathways in DM. These pathways involve wingless genes with Wnt, NAD^+ precursors with nicotinamide, forkhead transcription factors of the “O” class, and the cytokine and growth factor erythropoietin (EPO), each of which determine cellular development, survival and injury mechanisms, and longevity.

Novel cellular pathways and diabetes

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 [53, 72, 175, 184]. Wnt proteins determine multiple cellular functions that involve 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 [185-198]. Recent work in clinical disease indicates that abnormalities in Wnt pathways, such

as with transcription factor 7-like 2 gene, may impart increased risk for type 2 DM in some populations [199-201] and have a strong association with the development of obesity [202] (Table 1). The family member Wnt5b 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 [203]. In addition, clinical studies in patients with coronary artery disease and the combined metabolic syndrome with hypertension, hyperlipidemia, and DM have shown impaired Wnt signaling through a missense mutation in LRP-6 [204]. Experimental studies in mice with hyperglycemia through a high fat diet also show increased expression of Wnt3a and Wnt7a [205].

It also has been suggested that intact Wnt family members may offer glucose tolerance and increased insulin sensitivity [206] as well as protect glomerular mesangial cells from elevated glucose induced apoptosis [207]. Animals that over express Wnt10b with a high-fat diet experienced a reduction in bodyweight, hyperinsulinemia, triglyceride plasma levels, and improved glucose homeostasis [208]. Cell culture studies demonstrate that the Wnt1 protein that can be controlled by the growth factor EPO is necessary and sufficient to impart cellular protection during elevated glucose exposure [72, 209, 210]. EPO 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. In addition, blockade of Wnt1 with a Wnt1 antibody can neutralize the protective capacity of EPO, illustrating that Wnt1 is a critical component in the cytoprotection of EPO during elevated glucose exposure [72].

Wnt may foster cellular protection during DM through the novel regulation of protein kinase B (Akt) (Table 1). Activation of Akt can promote cell survival, such as during cell proliferation [211], progenitor cell development [169], blood-brain barrier permeability [212], inflammation [163, 213]. Ischemic-preconditioning [214], neurodegeneration [103], hyperglycemia [67, 215], hypoxia [216], amyloid toxicity [52, 53, 131, 132, 217], excitotoxicity [95], amyloid production [218], cardiomyopathy [219], cellular aging [220], and oxidative stress [145, 171, 221]. Akt activation also can modulate microglial cell activation [145, 171, 180], regulate transcription factors [222], maintain mitochondrial membrane potential ($\Delta\Psi_m$), prevent cytochrome c release [150, 180, 223], and block caspase activity [180, 216, 223]. However, as a “pro-survival pathway”, it should be recognized that Akt activation may be deleterious, such as during cancer resistance to chemotherapy [224].

A number of observations support the dependence of Wnt on Akt activation and support the premise that Wnt can modulate DM complications through Akt [192, 225, 226]. For example, neuronal cell differentiation requires Wnt signaling and trophic factor induction through Akt activity [227] and differentiation of cardiomyocytes proceeds only with Akt activation [228]. Wnt also has been shown in preadipocytes to increase Akt phosphorylation [229] and the Wnt-induced secreted protein in a fibroblast cell line uses Akt to block apoptotic death [230]. Secreted Frizzled-related proteins (sFRPs), which can modulate Wnt signaling, also employ Akt for cardiac tissue repair [231], reduction in tissue injury during pressure overload cardiac hypertrophy is tied to Akt activation [232], and cardiac ischemic preconditioning appear to rely upon Akt [233]. In the neuronal system, Wnt over-expression can independently increase the phosphorylation and the activation of Akt to promote neuronal protection. Inhibition of the phosphatidylinositol 3-kinase (PI 3-K) pathway or gene silencing of Akt expression prevents Wnt from blocking apoptotic injury and microglial activation [53].

Nicotinamide

As the amide form of vitamin B_3 (niacin), nicotinamide or nicotinic acid which is the water soluble form vitamin B_3, is obtained through synthesis or as a dietary source and supplement [234]. The principal form of niacin in dietary plant sources is nicotinic acid that is rapidly absorbed through the gastrointestinal epithelium [235]. Nicotinamide is subsequently

generated through the conversion of nicotinic acid in the liver or through the hydrolysis of NAD^+ [62]. After nicotinamide is obtained in the body, it functions as the precursor for the coenzyme ß-nicotinamide adenine dinucleotide (NAD^+) [61, 236] and also is essential for the synthesis of nicotinamide adenine dinucleotide phosphate ($NADP^+$) [237]. Initially, nicotinamide is changed to its mononucleotide form (NMN) with the enzyme nicotinic acid/nicotinamide adenylyltransferase yielding the dinucleotides $NAAD^+$ and NAD^+. $NAAD^+$ also yields NAD^+ through NAD^+ synthase [238] or NAD^+ can be synthesized through nicotinamide riboside kinase that phosphorylates nicotinamide riboside to NMN [239, 240].

The cellular pathways of nicotinamide are essential for energy metabolism and may directly impact normal physiology as well as disease progression [241-244]. Nicotinamide through NAD^+ has a critical physiological role in cellular metabolism and can be directly utilized by cells to synthesize NAD^+ [34, 61, 116]. 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 [245-247]. In addition, nicotinamide can significantly increase NAD^+ levels in vulnerable regions of the ischemic brain, suggesting that nicotinamide may prevent cell injury through the maintenance of NAD^+ levels [248]. During axonal degeneration, nicotinamide also may promote protection through NAD^+-dependent mechanisms [249]. Nicotinamide also appears to function directly at the level of mitochondrial membrane pore formation [61, 250, 251] to prevent the release of cytochrome c [252]. Nicotinamide can prevent mitochondrial membrane depolarization during exposure to either *tert*-butylhydroperoxide or atractyloside [253]. There are other mechanisms that nicotinamide may use to maintain cellular metabolic homeostasis through the maintenance of mitochondrial membrane potential [181, 250]. Nicotinamide can phosphorylate Bad [252] to prevent mitochondrial membrane depolarization and subsequent cytochrome c release. Nicotinamide also may inhibit the assembly of the mitochondrial permeability transition pore complex similar to the action of cyclosporin A [254] as well as stabilize cellular energy metabolism through ATP pathways [255].

In addition to its role in metabolism, nicotinamide can be essential for cellular differentiation, such as for human embryonic stem cells [256]. Nicotinamide has protean endocrine effects [257, 258], can scavenge ROS, and offers cellular protection for both neuronal [253, 259, 260] and vascular cells [34, 61, 116, 236]. In neuronal cell populations, nicotinamide protects against free radical injury [181], anoxia [261], excitotoxicity [262], homocysteine toxicity [263], ethanol-induced neuronal injury [264], and oxygen-glucose deprivation [253, 265]. In cortical neurons, nicotinamide blocks cell injury during ROS generating toxins such as tertiary butylhydroperoxide [266]. Nicotinamide also can protect both rod and cone photoreceptor cells against N-methyl-N-nitrosourea toxicity [267, 268] as well as against glycation end products in all layers of the retina [269]. In animal studies, nicotinamide improves cognitive function, cell survival, and reduces edema following cortical trauma [270-275], limits axonal degeneration [249], reduces cerebral ischemia [276-278] sometimes more effectively in models that were absent of comorbidities [279], prevents spinal cord injury [280, 281], and lessens disability in models of Parkinson's disease [100, 282, 283].

In regards to the vascular system [253, 259, 260], nicotinamide promotes vascular integrity [61, 116, 236] which may be crucial for tissue growth and repair [284]. Nicotinamide can protect the function of the blood brain barrier [270, 271], influence arteriolar dilatation and blood flow [285], increase skin vascular permeability [286], inhibit atherosclerotic plaque formation through inhibition of poly(ADP-ribose) polymerase [287], and foster platelet production through megakaryocyte maturation [288]. Nicotinamide can enhance endothelial cell viability during ROS exposure [181, 250, 261, 289]. Nicotinamide also may reverse a previously sustained early apoptotic injury [61, 181, 250, 252, 253, 261], suggesting that apoptosis prior to reaching genomic DNA degradation is dynamic and reversible in nature [61, 181, 251, 261]. Yet, some studies in

mice suggest that nicotinamide may either prevent or contribute to atherosclerotic plaques over a three to six month progression [290]. Although the mechanisms are not clear, it is conceivable that these events may occur during oxidative stress and the production of acidosis-induced cellular toxicity [291-293]. Nicotinamide cannot prevent cellular injury during intracellular acidification paradigms [181].

Since nicotinamide is closely aligned with cellular energy management, it may play a significant role during DM and the complications of this disorder (Table 1). For example, nicotinamide appears to have a close relationship with metabolic pathways that may lead to clinical cognitive changes [294]. Nicotinamide also has been shown to maintain normal fasting blood glucose with streptozotocin-induced DM in animal models [295, 296]. Nicotinamide can limit peripheral nerve injury during elevated glucose [297], reverse Type 1 DM in mice with acetyl-lcarnitine [298], and block oxidant stress [242, 250, 252, 264, 299]. Nicotinamide also affects levels of O-N-acetylglucosamin(O-GlcNAc)ylated proteins [300] and can significantly improve glucose utilization, prevent excessive lactate production in ischemic animal models [301]. In clinical conditions, oral nicotinamide administration, nicotinamide (1200mg/m^2/day) protects β-cell function and prevents clinical disease in islet-cell antibody-positive first-degree relatives of Type 1 DM [302]. Nicotinamide administration (25mg/kg) has been shown in patients with recent onset Type 1 DM combined with intensive insulin therapy for up to two years after diagnosis to reduce HbA_{1c} levels [303]. Also relevant to patients with DM and renal insufficiency, nicotinamide can reduce intestinal absorption of phosphate and prevent the development of hyperphosphatemia [304]. As a caveat for caution, some studies have reported that prolonged exposure to nicotinamide may lead to impaired β-cell function and reduction in cell growth [305, 306] as well as elevated nicotinamide levels may foster DM [307]. Furthermore, nicotinamide also may inhibit P450 and hepatic metabolism [308] and play a role in the progression of other disorders such as Parkinson's disease [283].

One novel pathway that may control some of the beneficial effects of nicotinamide during DM involves the forkhead transcription factors of the “O” class (FoxOs) [309, 310] (Table 1). These transcription factors either inhibit or activate target gene expression by binding bind to DNA through the forkhead domain that relies upon fourteen protein-DNA contacts [309, 311-314]. The term for these transcription factors is derived in part from imaging studies. On X-ray crystallography [315] or nuclear magnetic resonance imaging [316], the forkhead domain is described as a “winged helix” as a result of a butterfly-like appearance. 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 [317]. The current 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 [318]. Members of this family that include FoxO1, FoxO3, FoxO4, and FoxO6 are found throughout the body [82, 191, 317]. 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 [157, 313, 314, 319]. Modulation of FoxOs is a viable therapeutic target for systems that involve metabotropic glutamate receptors [96], neurotrophins [320], cancer [157, 313, 321], and cytokines [222] to foster intended cell survival.

Interestingly, FoxO proteins can modulate cell cycle progression to prevent tumor growth [157, 313, 322]. For example, administration of the Bcr-Abl tyrosine kinase inhibitor imatinib in chronic myelogenous leukemia cell lines blocks cell proliferation and promotes apoptotic cell death through FoxO3a and increased TRAIL production [323]. The transcription factor E2F-1 that that oversees cell cycle progression increases expression of FoxO1 and FoxO3a to lead to cell cycle arrest [324]. Other work indicates that FoxO proteins utilize the p53

upstream regulator p19(Arf) through Myc to block cell cycle induction and lymphoma progression [325].

Since attempted initiation of the cell cycle such as in neurons may be detrimental and can lead to cell death [49, 50, 326, 327], one may consider the ability of FoxO proteins to block cell cycle progression to be beneficial in these circumstances. In regards to cell metabolism and 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 [328]. In addition, adipose tissue-specific expression of Foxo1 in mice improves glucose tolerance and sensitivity to insulin during an elevated fat diet [329]. FoxO proteins also may protect against diminished mitochondrial energy levels known to occur during insulin resistance such as in the elderly populations [2, 3, 8]. In caloric restricted mice that have decreased energy reserves, Foxo1, Foxo3a, and Foxo4 mRNA levels were noted to progressively increase over two years [330]. 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 [331].

However, the role of FoxO proteins in different cell systems can be variable and do not consistently 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 [55, 75], illustrating that targeting FoxO3a activity may limit apoptotic caspase activity and promote cell survival (Figure 1). In clinical conditions, analysis of the genetic variance in *FOXO1a* and *FOXO3a* on metabolic profiles, age-related diseases, fertility, fecundity, and mortality in patients have observed higher HbA_{1c} levels and increased mortality risk associated with specific haplotypes of *FOXO1a* [332]. These clinical observations may indicate that elevated glucose levels can reduce post-translational phosphorylation of FOXO1, FOXO3a, and FOXO4 and initiate cellular apoptosis [333]. In addition, mice with a constitutively active Foxo1 transgene have increased microsomal triglyceride transfer protein and high plasma triglyceride levels [334]. Increased transcriptional activity of FoxO1, such as by the Sirt1 activator resveratrol, also can decrease insulin mediated glucose uptake and result in insulin resistance [335]. Overexpression of Foxo1 in skeletal muscles of mice can lead to reduced skeletal muscle mass and poor glycemic control [336]. Other studies that block the expression of Foxo1 in normal and cachectic mice [337] or reduce FoxO3 expression [338] demonstrate positive effects with an increase in skeletal muscle mass or resistance to muscle atrophy.

As the pathways with cellular metabolism and FoxOs begin to unravel, nicotinamide becomes an attractive agent to consider for DM [61, 62, 116, 236]. Nicotinamide inhibits FoxO protein activity through phosphorylation [253] and may be protective through two separate mechanisms of post-translational modification of FoxO3a [35, 157, 191, 314, 317]. Nicotinamide not only can maintain phosphorylation of FoxO3a and inhibit its activity to potentially block caspase 3 activity [253], but also can preserve the integrity of the FoxO3a protein to block FoxO3a proteolysis that can yield pro-apoptotic amino-terminal fragments [253]. During oxidative stress, an initial inhibitory phosphorylation of FoxO3a at the regulatory phosphorylation sites (Thr^{32} and Ser^{253}) occurs [253, 339]. Yet, loss of phosphorylated FoxO3a expression appears to subsequently result over twelve hours, possibly by caspase degradation, which can raise the vulnerability of neurons to apoptotic injury [253]. The loss of both FoxO3a phosphorylation and the integrity of this transcription factor may then lead to apoptosis. FoxO3a proteolysis occurs during cell injury yielding an amino-terminal (Nt) fragment that can become biologically active and lead to cellular injury [340]. Nicotinamide, through the phosphorylation of FoxO3a blocks apoptotic cell injury and prevents caspase 3 activity [253].

Nicotinamide is closely linked to cell longevity pathways that involve not only FoxOs, but also sirtuins [116, 341, 342]. FoxO proteins are deacetylated by histone deacetylases. These include the sirtuin Sirt1, a NAD^+-dependent deacetylase and the mammalian ortholog of the silent information regulator 2 (Sir2) protein [310], that can control multiple processes such as cell injury, lifespan, and metabolism [343, 344]. FoxO proteins and sirtuins have been associated with cell longevity and aging as shown by early studies linking DAF-16 in *Caenorhabditis elegans* [157, 310, 344-346]. Furthermore, sirtuins are tied to cellular metabolism [343, 347] and increased cell survival [344, 345, 348-350]. Yet, the relationship among nicotinamide, FoxO transcription factors, and sirtuins is not entirely clear (Table 1). For example, some studies suggest that stimulation of Sirt1 during starvation is dependent upon FoxO3a activity as well as p53 [351]. During exercise, an up-regulation of FoxO3a and Sirt1 activity is observed in the heart of rats [352], suggesting that physical activity may be beneficial for the cardiovascular system through FoxO proteins. Other work has shown that Sirt1 may repress the activity of FoxO1, FoxO3a, and FoxO4, illustrating that cellular longevity may benefit from reduction in FoxO protein generated apoptosis [353].

However, nicotinamide prevents oxidant-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 [268] and in cell culture models [61, 181, 250]. In contrast to these cytoprotective concentrations of nicotinamide that also can modulate offers gene regulation [354], a reduction in nicotinamide levels during nicotinamidase expression supports increased cellular survival and longevity [348, 350]. Nicotinamide can block cellular Sir2 by intercepting an ADP-ribosyl-enzyme-acetyl peptide intermediate with the regeneration of NAD^+ (transglycosidation) [355]. Physiological concentrations of nicotinamide noncompetitively inhibit Sir2, suggesting that nicotinamide is a physiologically relevant regulator of Sir2 enzymes [356]. Interestingly, 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 [348, 350]. 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, in relation to cell longevity, 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 [250, 252, 253, 261, 348, 350, 357], at least in yeast and metazoans [116, 341, 342]. Sirtuins also may prevent nicotinamide from assisting with DNA repair by altering the accessibility of DNA damaged sites for repair enzymes [358]. Furthermore, sirtuin activators, at least at the experimental animal level, may promote glucose homeostasis and insulin sensitivity [62, 343, 344, 350, 359] while also reducing the risk of obesity [360].

Erythropoietin

The growth factor and cytokine EPO is approved by the Food and Drug Administration for the treatment of anemia, but continued new work has identified this agent for the potential treatment of multiple disorders [209, 361]. Clinical considerations include treatment for depression [362], Alzheimer's disease [52, 363, 364], Parkinson's disease [365], immune system dysfunction [150, 222, 223, 366, 367], neurodegeneration [52, 71, 150, 223, 368-371], cardiovascular disorders [180, 216, 222, 372-379], spinal cord injury [380, 381], brain edema [382], fertility [383], trauma [384-386], shock [387-389], infection [390-392], pulmonary disease [393-395], renal disease [68, 396-398], gastrointestinal disorders [399-401], ocular disease [402-404], and metabolic disorders [2, 33, 34, 71, 72, 405]. New studies further support the use of intravitreal EPO injections in patients [406].

EPO is required for erythropoiesis [407-409], but also functions in other organs and tissues, such as the brain, heart, and vascular system [216, 222, 223, 410-412]. EPO production is believed to occur throughout the body [83, 361, 413] and can be detected in the breath of healthy individuals [414]. The principal organs of EPO production and secretion are the kidney, liver, brain, and uterus [210, 339, 415].

In regards to EPO during DM, plasma EPO is often low in diabetic patients with anemia [416] or without anemia [417]. The inability of these individuals to produce EPO in response to a declining hemoglobin levels suggests an impaired EPO response during DM [418] (Table 1). Yet, increased EPO secretion during diabetic pregnancies may represent the body's attempt at endogenous protection against the complications of DM [419, 420]. This potential cytoprotective capacity of EPO may be important during complications of DM, such as those that involve cognitive impairment. For example, EPO may improve cognitive ability. EPO may reduce in animal models apoptotic pathways during periods of hyperoxia in the developing brain [421, 422]. Furthermore, clinical disorders may have periods of hyperoxia followed by cerebral hypoperfusion and hypoxia that can lead to cerebral injury with associated oxidative stress [423]. EPO under these conditions also may be protective since it can promote neurite outgrowth [424] and also may regulate hemoglobin levels that have recently been associated with cognitive decline [425]. Elevated EPO concentrations during infant maturation have been correlated with increased Mental Development Index scores [426] and EPO may prevent toxic effects of agents used to control cognitive function such as haloperidol [427].

In relation to clinical relevance, 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 [428] (Table 1). In addition, EPO can serve to reverse the complications of anemia during DM [33]. Experimental work during elevated glucose also has demonstrated that EPO can significantly improve vascular cell survival in a 1.0 ng/ml range [72]. 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 [429, 430], illustrating that the effects of EPO observed during *in vitro* studies may parallel the cellular processes altered by EPO in patients with DM [426].

Protection in the hematological and vascular system by EPO may rely upon modulation of FoxOs and Wnt signaling [209, 361] (Table 1). EPO fosters eythroid progenitor cell development through the regulation of FoxO activity [361, 413, 431] and may require regulation of specific gene expression through an EPO-FoxO3a association to promote erythropoiesis in cultured cells [432]. In addition, EPO exerts cellular protection through Wnt signaling. Cell culture studies demonstrate that the Wnt1 protein is necessary and sufficient to impart cellular protection during elevated glucose exposure [72]. EPO 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. In addition, blockade of Wnt1 with a Wnt1 antibody can neutralize the protective capacity of EPO, illustrating that Wnt1 is a critical component in the cytoprotection of EPO during elevated glucose exposure [72]. Furthermore, EPO during elevated glucose and similar to other models of oxidative stress can block neuronal degeneration [71], prevents renal cell apoptosis [405], apoptotic DNA degradation, and degeneration in cardiac and vascular cell models [180, 216, 222, 411, 433]. Protection by EPO also is related to the maintenance of mitochondrial membrane potential, since loss of mitochondrial membrane potential is known to lead to apoptotic cell injury [166, 434]. EPO has the capacity to prevent the depolarization of the mitochondrial membrane that also affects the release of cytochrome c [150, 216, 435] (Figure 2).

Biomarkers and future considerations

Primary cellular pathways that may be critical for the development of new drug therapies also may possess great utility to function as biomarkers that can predict the diagnosis, onset, or progression of disease. Biomarkers can be used for the determination of specific genes, proteins, or products of cellular and biological processes. In addition, biomarkers can represent the response of cells or tissues to therapeutic strategies [81]. Many of the biological outcomes described for Wnt, nicotinamide, and EPO encompass necessary cellular pathways for development, growth, and survival. Yet, these entities also hold the potential to further disease progression or be set in motion during disease onset as an endogenous protective response. In regards to Wnt, signaling for this glycoprotein may indicate the onset of early tissue injury during conditions such as elevated glucose [72], amyloid toxicity [53], or cardiac ischemia [233, 436] and alert the need for rapid responsive treatments to limit cell injury. Yet, increased Wnt expression also may suggest disease progression as well as a poor prognostic response to prior therapies [34, 177, 192]. Aberrant Wnt signaling has been associated with advanced prostate cancer and bone metastases [437], the genesis of cancer stem cells [185], the reliance of FoxO pathways to promote unregulated cell proliferation in cancer [438], and the vulnerability of patients with Type 2 DM to develop colorectal tumors [439].

Independent from Wnt, FoxOs and EPO may serve as essential biomarkers. For example, the absence of FoxO proteins can suggest tumor progression [440]. On the converse side, the up-regulation of FoxO proteins can indicate a positive response to chemotherapy [321, 441, 442] and also be an indicator and responsive agent to ischemic tissue [443]. In some scenarios, expression of FoxO proteins may suggest tissue protection and recovery, since FoxO3a activity may enhance vascular smooth muscle antioxidant properties in aged animals and be beneficial to the cardiovascular system during physical exertion [352]. In a similar manner, EPO also may be a positive indicator of cytoprotective responses [209, 210, 339]. Although EPO has not been shown to correlate with Psychomotor Development Index or an overall incidence of neurodevelopmental impairment, in clinical studies infants with elevated EPO possessed higher Mental Development Index scores than infants with lower EPO concentrations, suggesting that the presence of EPO may correlate with a positive developmental course. Advanced cognitive function also may rely upon appropriate levels of EPO that can be followed since both low and high levels of EPO in the elderly can be associated with diminished cognitive function [425]. Yet, the presence of EPO may affect a number of other systems in addition to the brain [444]. Recent work has shown that the presence of a truncated form of EPO receptor can function as a dominant negative regulator of EPO signaling and lead to hypertension, suggesting that monitoring of this biomarker may identify individuals susceptible to hypertension [445]. Although EPO has recently been reported to prevent drug-induced fibrosis and possible endothelial damage during chemotherapy [446], it is important to note that EPO also may foster tumor progression [447, 448]. EPO and its receptor are present in tumor specimens, may block tumor cell apoptosis through Akt [449], enhance metastatic disease, [450], and complicate radiotherapy by assisting with tumor angiogenesis [451].

Drug development for any disorder becomes a complex enterprise, especially for disorders such as DM with the multiple complications of this disease that can ensue through oxidant stress pathways. Nevertheless, elucidation of novel pathways and their biological role that have an intimate relationship with agents such as Wnt, nicotinamide, and EPO are vital for the successful treatment of clinical disease. In addition, defining the ability of these agents to function as potential biomarkers for disease can further enhance the utility of new entities irrespective of their treatment potential. Given that the present percentage of the gross domestic product for U.S. healthcare spending is the highest in the world, life expectancy in the U.S. trails behind other countries, and that the number of individuals affected by DM globally is expected to climb exponentially over the years, it becomes critical to understand

both the clinical efficacy of novel treatments as well as the potential complications of these agents especially in a variety of circumstances that may not only involve essential cellular repair but also undesirable cellular proliferation.

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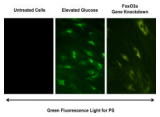

Figure 1. Transfection of FoxO3a siRNA in endothelial cells prevents apoptotic phosphatidylserine (PS) exposure during elevated D-glucose

Representative images illustrate that gene knockdown of *FoxO3a* with FoxO3a siRNA (siRNA) significantly blocks endothelial cell membrane PS externalization assessed by annexin V phycoerythrin (green fluorescence). FoxO3a siRNA alone was not toxic and non-specific scrambled siRNA did not reduce PS exposure during elevated D-glucose.

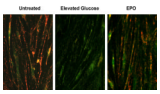

Figure 2. Erythropoietin (EPO) blocks mitochondrial depolarization during elevated D-glucose

Elevated D-glucose (20 mM) resulted in a significant decrease in the red/green fluorescence intensity ratio of mitochondria using a cationic membrane potential indicator JC-1 within 48 hours when compared with untreated endothelial cells, illustrating that elevated D-glucose leads to mitochondrial membrane depolarization. In contrast, pre-treatment with EPO (10 ng/ml) during elevated D-glucose significantly increased the red/green fluorescence intensity of mitochondria in endothelial cells, indicating that mitochondrial membrane potential was restored by EPO.

Table 1

Summary of Clinical Outcomes and Signaling Pathways with Wnt, Nicotinamide, and Erythropoietin

Therapeutic Presentation and Potential During Diabetes Mellitus (DM)	Clinical Outcomes	Signaling Pathways
Wnt	Wnt pathways, such as with transcription factor 7-like 2 gene, may impart increased risk for type 2 DM Wnt may have an association with the development of obesity Wnt has an elevated expression in adipose tissue, the pancreas, and the liver in patients with DM Impaired Wnt signaling through a missense mutation in LRP-6 during metabolic syndrome	Vascular/renal cell early and late apoptotic programs decreased by Wnt Wnt utilizes EPO for protection against elevated glucose Protection by Wnt through Akt and Secreted Frizzled-related protein pathways
Nicotinamide	Nicotinamide can maintain normal fasting blood glucose and improve glucose utilization in animal models of DM Nicotinamide can limit peripheral nerve injury during elevated glucose Nicotinamide protects β-cell function in islet-cell antibody-positive first-degree relatives of Type 1 DM Nicotinamide combined with intensive insulin therapy reduces HbA_{1c} levels Nicotinamide can reduce intestinal absorption of phosphate and prevent the development of hyperphosphatemia	Nicotinamide functions through transcription factors of the forkhead family and caspases Nicotinamide has an inverse relationship with sirtuins that can alter cell survival and cell longevity
Erythropoietin (EPO)	EPO is often low in DM, suggesting an impaired EPO response EPO in diabetic patients with severe, resistant congestive heart failure can decrease fatigue, increase left ventricular ejection fraction, and significantly decrease hospitalization stay EPO can serve to reverse the complications of anemia during DM EPO can protect vascular cells during DM	EPO protection in the hematological and vascular systems relies upon modulation of FoxO and Wnt EPO fosters eythroid progenitor cell development through FoxO activity EPO during elevated glucose and similar to other models of oxidative stress can block cell degeneration through Wnt Protection by EPO is governed by the maintenance of mitochondrial membrane potential