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Programming Apoptosis and Autophagy with Novel Approaches for Diabetes Mellitus

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Abstract

According to the World Health Organization, diabetes mellitus (DM) in the year 2030 will be ranked the seventh leading cause of death in the world. DM impacts all systems of the body with oxidant stress controlling cell fate through endoplasmic reticulum stress, mitochondrial dysfunction, alterations in uncoupling proteins, and the induction of apoptosis and autophagy. Multiple treatment approaches are being entertained for DM with Wnt1 inducible signaling pathway protein 1 (WISP1), mechanistic target of rapamycin (mTOR), and silent mating type information regulation 2 homolog) 1 (*S. cerevisiae*) (SIRT1) generating significant interest as target pathways that can address maintenance of glucose homeostasis as well as prevention of cellular pathology by controlling insulin resistance, stem cell proliferation, and the programmed cell death pathways of apoptosis and autophagy. WISP1, mTOR, and SIRT1 can rely upon similar pathways such as AMP activated protein kinase as well as govern cellular metabolism through cytokines such as EPO and oral hypoglycemics such as metformin. Yet, these pathways require precise biological control to exclude potentially detrimental clinical outcomes. Further elucidation of the ability to translate the roles of WISP1, mTOR, and SIRT1 into effective clinical avenues offers compelling prospects for new therapies against DM that can benefit hundreds of millions of individuals throughout the globe.

Keywords

AMPK; apoptosis; autophagy; cardiac; CCN; diabetes mellitus; erythropoietin; forkhead; FoxO; metformin; nervous system; oxidative stress; mTOR; sirtuins; SIRT1; stem cells; vascular; WISP1; Wnt

1. Introduction

Each year, metabolic disease impacts a significantly greater portion of the global population. Such observations appear to be in contrast to the high expenditures provided for healthcare in developed nations. For example, according to the Centers for Medicare and Medicaid Services (CMS) (1), the United States in the year 2012 spent 2.8 trillion on healthcare that was equal to $8, 915 per person and 17.2 percent of the Gross Domestic Product (GDP). Hospital care costs were increased 4.9 percent from the prior year to equal $882.3 billion

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and spending on physician and clinical services increased 4.6 percent to $565 billion. In addition, out of pocket spending per individual on healthcare in the year 2012 was estimated to have grown 4.1 percent to $320.2 billion. By the year 2022, healthcare spending is projected to be 19.9 percent of the GDP.

Contributing to these costs and the growing prevalence of metabolic disorders such as diabetes mellitus (DM) is the increased incidence of obesity in the population (2–6). Obesity leads to a number of metabolic disorders that includes cellular oxidative stress and insulin resistance (7, 8), lipid –induced dysfunction of pancreatic β cells (9), cellular inflammation (10), altered trophic factor release (11–14), and impairment in protein tyrosine phosphatase signaling (6, 15). Yet, it is the duration of obese-years rather than the body mass index (BMI) that corresponds to a strong risk for developing DM (16).

Given the increased presence and progressive contribution of risk factors such as obesity for metabolic disorders, DM also is growing at an exponential rate. The World Health Organization predicts that DM will be the seventh leading cause of death by the year 2030 (17). For the year 2013, 347 million individuals are believed to have DM and more than one million of these individuals are dying from the disease. In the United States, it is estimated that DM costs employers $69 billion in reduced productivity and another $176 billion for direct medical costs. At least 21 million individuals are diagnosed with DM in the US and another 8 million individuals are estimated to be undiagnosed with DM (18). A strong case can be made for clinical programs that assist with the early diagnosis of DM given that a significant portion of the population currently remains undiagnosed with DM (10, 19). Furthermore, the incidence of impaired glucose tolerance in the young also raises additional concerns (3). Individuals with impaired glucose tolerance have more than twice the risk for the onset of diabetic complications than individuals with normal glucose tolerance (20).

DM is considered to be either non-insulin dependent (Type 1) or insulin dependent (Type 2) (21). Type 1 DM occurs in approximately 5–10% of DM patients. It is an autoimmune disorder with the presence of alleles of the human leukocyte antigen (HLA) class II genes within the major histocompatibility complex (MHC) (22). Destruction of pancreatic β-cells with inflammatory infiltration of the islets of Langerhans leads to the loss of insulin production and regulation. Activation of T-cell clones that are capable of recognizing and destroying β-cells can result in severe insulin deficiency. T-cell clones escape thymus control that yields high affinity for MHC molecules with T-cell receptors, but these clones have incorrect low affinity for self-peptides. Once released into the body, these T-cell clones can become activated to destroy self-antigens. Almost 90% of patients with Type 1 DM have increased titers of autoantibodies (Type 1A DM). The remaining 10% of Type 1 DM individuals do not have serum autoantibodies. These individuals are considered to have maturity-onset diabetes of the young (MODY) that can be a result of β-cell dysfunction with autosomal-dominant inheritance (Type IB DM).

Type 2 DM occurs in approximately 90% of individuals most notably in individuals over the age of 40 and has a progressive deterioration of glucose tolerance with early β-cell compensation (23). Initial cell hyperplasia is followed by a decrease in pancreatic β-cell mass with subsequent insulin resistance and impairments in insulin secretion occurring.

Defective insulin secretion can result from impaired β-cell function, chronic exposure to free fatty acids and hyperglycemia, as well as the absence of inhibitory feedback through plasma glucagon levels. Interestingly, Type 1 and Type 2 DM may have common links since approximately 10% of individuals with Type 2 DM may have elevated serum autoantibodies similar to Type 1 DM and insulin resistance also may be a component of Type 1 DM in some patients.

2. DM, Involvement of Multiple Organ Systems, and Oxidative Stress

DM can injure multiple organ systems throughout the body. As a result, DM has been reported to lead to vascular disease (24–30), cardiac disorders (31–39), renal disease (2, 40–43), hepatic disorders (44–49), and immune cell impairment (38, 50–54). In the neurovascular arena, DM can contribute to cognitive loss through acute stroke onset (55). During chronic neurodegenerative disorders that involve Alzheimer's disease with DM (22, 56), insulin resistance has been reported in patients with Alzheimer's disease that links impaired cellular metabolism with cognitive loss (57–59). DM also leads to neuropsychiatric disorders (60, 61), peripheral nerve disorders (27), and retinal disease (62–64). At the vascular cell level, elevated glucose levels reflective of those that occur during DM can result in endothelial cell senescence (25), impaired mobilization of endothelial progenitor cells from the bone marrow (65), neuroglialvascular unit compromise (62), inhibition of angiogenesis (26), and loss of endothelial cells (14, 30, 66–70).

Oxidative stress is an important determinant of cell injury in DM (4, 21, 71–76). Oxidant stress that results in the generation of reactive oxygen species (ROS) can significantly affect cellular metabolism and lead to cell injury during DM (77, 78) and contribute to disability that involves impaired cognitive function (79–81), cerebral ischemia (77, 82), and epigenetic linked disease (83–87). ROS are formed through superoxide free radicals, hydrogen peroxide, singlet oxygen, nitric oxide (NO), and peroxynitrite that lead to mitochondrial dysfunction, loss of DNA integrity, cellular dysfunction, and protein misfolding (21, 76, 88–91). Endogenous antioxidant systems can limit the generation of ROS and include catalase, superoxide dismutase, glutathione peroxidase, and vitamins C, D, E, and K (23, 75, 85, 90, 92–100).

Yet, excessive production of ROS or impairments in the endogenous antioxidant system such as those that can occur during DM can ultimately lead to oxidative stress and cell death (8, 22, 23, 27, 29, 63, 74, 76, 101). In murine animal models of Type 2 DM, oxidative stress results in elevated glutathione levels and increased lipid peroxidation (33). Advanced glycation end products (AGEs), entities that promote complications in DM (32, 36), also result in the release of reactive oxygen species (ROS) and caspase activation (74). In experimental cell models, exposure to elevated glucose levels foster oxidant stress mechanisms that lead to cell injury in cardiomyocytes (35, 39, 102), neurons (55, 63, 69, 103, 104), and endothelial cells (62, 65–68, 105). Elevations in serum glucose also can increase antioxidant enzyme levels in human endothelial cells, suggesting that some cells can attempt a reparative process during oxidative stress exposure (106). In clinical studies, patients with Type 2 DM display serum markers of oxidative stress with ischemia-modified albumin (107). However, chronic hyperglycemia during DM is not necessary to lead to

oxidative stress injury, since even brief periods of hyperglycemia generate ROS (108). Clinical correlates show that both acute glucose swings as well as chronic hyperglycemia can trigger oxidative stress mechanisms during Type 2 DM (109).

Oxidative stress during DM also leads to mitochondrial dysfunction, endoplasmic reticulum stress, and alterations in uncoupling proteins (UCPs) (72, 110). ROS exposure during DM can result in the opening of the mitochondrial membrane permeability transition pore, reduce mitochondrial NAD^+ stores, activate cytochrome c release, and initiate caspase activity (29, 66, 68, 70, 105, 111, 112). Exposure of glucolipotoxicity caused by elevated plasma glucose and lipid levels to pancreatic β-cells promotes oxidative stress with cytochrome c release, caspase activation, and apoptosis (111). High fat diets (113) as well as free fatty acid release that occurs during DM have been shown to release ROS, lead to mitochondrial DNA damage, and impair pancreatic β-cell function (114). Subsequently, mitochondrial dysfunction and cell death leads to apoptosis and autophagy (63). In patients with Type 2 DM, skeletal muscle mitochondria have been reported to be smaller than those in control subjects (115). A decrease in the levels of mitochondrial proteins and mitochondrial DNA in adipocytes also has been associated with the development of Type 2 DM (116). “Highly-oxidized glycated” low density lipoproteins that can occur in DM also result in oxidative and endoplasmic reticulum stress in human retinal capillary pericytes (63).

In addition to the role that mitochondria play during oxidative stress and DM, UCPs are a significant component in modulating cell survival in DM (72, 110, 117). UCPs are a family of carrier proteins found in the inner membrane of mitochondria and consist of the mammalian members UCP-1, 2,3,4,5 (118). UCPs uncouple oxygen consumption through the respiratory chain from ATP synthesis and can lead to the generation of ROS. UCPs disperse a proton electrochemical potential gradient across the mitochondrial inner membrane resulting in the activation of substrate oxidation and dissipation of oxidation energy as heat instead of ATP (72, 110). In addition, UCP family members also can influence insulin sensitivity. Uncoupling of respiration by UCPs plays a role in regulating ATP synthesis, fatty acid release, and glucose oxidation. For example, UCP1 may have beneficial effects during DM. Muscle-specific overexpression of UCP for skeletal muscle can increase energy expenditure and enhance insulin sensitivity to protect in animal models from high-fat diet induced insulin resistance (119). Skeletal muscle respiratory uncoupling also can enhance insulin sensitivity in obesity (120). Yet, other UCPs such as UCP2 may have detrimental effects. Overexpression of UCP2 in isolated pancreatic islets results in decreased ATP levels and blunted glucose-stimulated insulin secretion. Deletion UCP2 improves insulin secretion and decreases hyperglycemia in leptin-deficient mice (121). In relation to other UCP members during DM, UCP3 can stimulate insulin uptake (122) and may function to facilitate fatty acid oxidation and minimize ROS production (123).

3. DM, Apoptosis, and Autophagy

The programed cell death pathways of apoptosis (4, 23, 27, 70, 75, 124) as well as autophagy (2, 21, 125, 126) play significant roles during DM and oxidative stress (127). Necroptosis, another pathway involved in programmed cell death, does not presently appear

to contribute significantly to cell survival in DM (128), but further published work may change these observations. Recent studies in murine models of Type 1 DM suggest that necroptosis may have less than an essential role in cell death during DM (129).

Apoptosis can oversee tissue development and remodeling during early stages of development, but in mature cells and tissues, the induction of apoptosis can lead to cell death during DM (4, 125). Apoptosis consists of both an early phase that involves the loss of plasma membrane lipid phosphatidylserine (PS) asymmetry and a later phase that leads to genomic DNA degradation (79, 130–132). Since the early phase of apoptosis with membrane PS externalization alerts inflammatory cells to engulf and remove injured cells, prevention of membrane PS externalization is vital to block the loss of functional cells that may become temporarily disabled (21). In DM, apoptosis can lead to neuronal injury (60, 103, 104, 133), cardiomyocyte destruction (34, 35, 38), pancreatic β-cell loss (134–136), endothelial cell injury (25, 26, 67, 105, 137), and renal cell dysfunction (138–140).

In regards to autophagy during DM, this pathway of programmed cell death may have variable outcomes (141). Autophagy recycles cytoplasmic components and discards defective organelles for tissue remodeling (125, 142). During DM, the sub classification of macroautophagy plays a principal role and involves the sequestration of cytoplasmic proteins into autophagosomes that fuse with lysosomes for degradation and recycling for future cellular processes (2, 29). Autophagy may be cytoprotective during DM. Recent work suggests that loss of autophagy may foster the progression from obesity to DM, since autophagy haploinsufficiency in murine animal models of obesity can lead to increased insulin resistance with elevated lipids and inflammation (143). Autophagy also may be required to eliminate misfolded proteins and non-functioning mitochondria to avert β-cell dysfunction and the onset of DM (144). Exercise in mice also has been shown to initiate autophagy and regulate glucose homeostasis (145). These results may be associated with observations that autophagy has been reported to improve insulin sensitivity during high fat diets in mice (8). Pathways of autophagy and apoptosis also may complement one another to control cell survival. For example, induction of autophagy may protect cardiomyocytes from apoptotic cell death during DM (34).

However, it should be noted that autophagy might not be consistently beneficial (128, 141, 146). Under some conditions, autophagy may be less of a prominent modulator of cell survival than apoptosis in some experimental models (147). In addition, during elevated glucose exposure, autophagy has been shown to impair endothelial progenitor cells, lead to mitochondrial oxidative and endoplasmic reticulum stress (148), and prevent the formation of new blood vessels (29). Increased activity of autophagy also has been associated with significant loss of cardiac and liver tissue in diabetic rats during attempts to achieve glycemic control through diet modification (149). During periods of elevated glucose, AGEs have been shown to lead to the induction of autophagy and vascular smooth muscle proliferation that can result in atherosclerosis (28) as well as cardiomyopathy (102).

4. WISP1 and DM

Multiple pathways can result in cellular injury through oxidative stress mechanisms during DM. As a result, recent investigations have concentrated upon pathways that involve anti-oxidant therapies (3, 23, 27, 30, 53, 71, 75), mammalian forkhead transcription factors (9, 37, 47, 150, 151), protein tyrosine phosphatases (6, 15, 152), and growth factors (11–13, 50, 65, 70, 104). In addition, new therapeutic strategies are now focusing upon the role of extracellular matrix associated proteins such as the CCN family of proteins (153, 154). The CCN family of proteins consists of six secreted extracellular matrix associated proteins. This family is defined by the first three members of the family that include Cysteine-rich protein 61, Connective tissue growth factor, and Nephroblastoma over-expressed gene (155). The CCN family members contain four cysteine-rich modular domains that include insulin-like growth factor-binding domain, thrombospondin domain, von Willebrand factor type C module, and C-terminal cysteine knot-like domain.

Of the CCN family members, Wnt1 inducible signaling pathway protein 1 (WISP1) is increasingly being recognized as a potential target for the complications tied to DM (Fig. 1). The *WISP1* gene was identified in a mouse mammary epithelial cell line (156) and later shown to modulate gastric tumor growth (157). WISP1 is a target of the *wingless* pathway Wnt1, a cysteine-rich glycosylated protein that can modulate neuronal development, angiogenesis, bone growth, immune cell modulation, tumorigenesis, programmed cell death, and stem cell proliferation (158–170). WISP1 is present in a multiple sites throughout the body including the epithelium, heart, kidney, lung, pancreas, placenta, ovaries, small intestine, spleen, and brain (125). WISP1 is a matricellular protein that alters the signaling of other pathways to impact processes such as programmed cell death, extracellular matrix production, cellular migration, and mitosis (171). Early work highlighted that WISP1 can block p53 mediated DNA damage and prevent the induction of apoptosis (172). Yet, WISP1 also can control other pathways of programmed cell death such as autophagy (125, 147) as well as apoptosis (172–175) and caspase activation (173, 174, 176).

WISP1 drives cellular proliferation and survival through several pathways that involve phosphoinositide 3 –kinase (PI 3-K), protein kinase B (Akt), sirtuins, and the mechanistic target of rapamycin (mTOR) (21, 153, 177). WISP1 can up-regulate PI 3-K and Akt during oxidative stress (147, 174, 176), DNA damage (172), fibroblast proliferation in airway remodeling (178), cardiomyocyte injury (173), vascular smooth muscle proliferation (179), and toxic β-amyloid (Aβ) exposure (180). Through Akt activation, WISP1 leads to the inhibitory phosphorylation of glycogen synthase kinase -3β (GSK-3β) (147, 173, 176, 178) that maintains the integrity of β-catenin and allows translocation of this protein to the cell nucleus to block apoptotic cell death (159, 164, 181–185).

WISP1 cellular protection also relies upon sirtuin and mTOR mediated pathways. Sirtuins are histone deacetylases that transfer acetyl groups from ε-N-acetyl lysine amino acids on the histones of DNA to regulate transcription (10, 131, 186–190). In regards to silent mating type information regulation 2 homolog) 1 (*S. cerevisiae*) (SIRT1), a member of the sirtuin family that can modulate cellular metabolism during DM (44, 54, 191, 192), WISP1 increases SIRT1 activity and promotes SIRT1 nuclear translocation (174) that results in the

blockade of apoptotic injury (105, 193, 194). WISP1 controls the mammalian forkhead transcription factor FoxO3a, a mediator of cellular metabolism as well as caspase activity (9, 37, 47, 150, 151) to maintain the integrity of SIRT1 during oxidative stress (174).

With mTOR, WISP1 can activate this pathway and phosphorylate the mTOR down-stream components of p70 ribosomal S6 kinase (p70S6K) and the eukaryotic initiation factor 4E-binding protein 1 (4EBP1) (32, 195). In addition, WISP1 increases mTOR activity by blocking the inhibitory actions of the mTOR component proline rich Akt substrate 40 kDa (PRAS40) (196). WISP1 also oversees the post-translational phosphorylation of AMP activated protein kinase (AMPK) that is involved in glucose homeostasis (197–200) to control the activity of this protein as well as mTOR. AMPK regulates the activity of the hamartin (tuberous sclerosis 1)/tuberin (tuberous sclerosis 2) (TSC1/TSC2) complex that is an inhibitor of the mTOR complex mTOR Complex 1 (mTORC1) (201). When active, AMPK phosphorylates TSC2 as well as Raptor to block the activity of mTOR and the complex mTORC1 during energy stress (202). WISP1 modulates AMPK activation by differentially decreasing phosphorylation of TSC2 at Ser^{1387}, a target of AMPK, and increasing phosphorylation of TSC2 at Thr^{1462}, a target of Akt (180). As a result, WISP1 increases TSC2 activation with concurrent limits placed upon AMPK activation. For proper cellular function and survival with WISP1, a minimal level of TSC2 and AMPK activity is necessary (180). The ability of WISP1 to modulate AMPK activity is critical for proper cellular metabolism during DM (200). In some cases, AMPK activity can lead to a reduction in insulin resistance and diminished oxidative stress mediated through activation of autophagy (8). In addition, AMPK may limit myocardial ischemia in experimental models of DM (203), promote proper metabolic function of cells (204), and block adipocyte differentiation, lipid accumulation, and obesity (205). However, the level of AMPK activity may be an important consideration in DM since in some experimental models of Type 2 DM, AMPK activation can lead to apoptosis in pancreatic islet cells (206).

The reparative processes of WISP1 that involve DM also may be linked to stem cell proliferation, migration, and differentiation. Expression of WISP1 is increased during stem cell migration (207). WISP1 can influence induced pluripotent stem cell reprogramming (208, 209). In relation to cellular metabolism, WISP1 is differentially regulated during human embryonic stem cell and adipose-derived stem cell differentiation. WISP1 is up-regulated during human adipocyte differentiation (154), in human embryonic stem cells, and is repressed in adipose-derived stem cells during hepatic differentiation (210). Furthermore, in studies that examine pancreatic regeneration, WISP1 is one of several genes that are over-expressed during this process, suggesting that WISP1 may control a protective process during DM (211). WISP1 may be critical for the development of therapeutic strategies against vascular complications of DM. WISP1 expression is selectively up-regulated and may support vascular repair and regeneration during saphenous vein crush injury (212). WISP1 also promotes vascular smooth muscle proliferation that may be important for tissue repair during injury or affect restenosis following vascular grafting (179, 213). Importantly, WISP1 can lead to cellular senescence (214) and does not appear to foster excessive cellular proliferation in aging vascular cells (215) that may result in the development of atherosclerosis. As a potential endogenous reparative response to injury, WISP1 expression

is affected by weight change in humans and increases during insulin resistance and inflammation in glucose-tolerant individuals (154).

5. mTOR and DM

As noted with some of the metabolic pathways linked to WISP1, mTOR is one of the principal pathways necessary for the control of aging and cellular metabolism during DM (4, 199, 216) (Fig. 1). Also known as the mammalian target of rapamycin and FK506-binding protein 12-rapamycin complex-associated protein 1, mTOR is a 289-kDa serine/threonine protein kinase that is encoded by a single gene *FRAP1* (217–219). mTOR is a component of the protein complexes mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2) (197, 199). mTORC1 is composed of Raptor (Regulatory-Associated Protein of mTOR), the proline rich Akt substrate 40 kDa (PRAS40), Deptor (DEP domain-containing mTOR interacting protein), and mLST8/GβL (mammalian lethal with Sec13 protein 8, termed mLST8). In contrast, mTORC2 is composed of Rictor (Rapamycin-Insensitive Companion of mTOR), Deptor, mLST8, the mammalian stress-activated protein kinase interacting protein (mSIN1), and the protein observed with Rictor-1 (Protor-1) (199, 220).

mTOR can influence both apoptotic and autophagic pathways of programmed cell death (221). In relation to cellular metabolism and DM, mTOR activation through glucagon-like peptide-1 agonists can protect pancreatic β-cells from cholesterol mediated apoptotic cell injury (222), promote pancreatic β-cell proliferation (136), and block neural apoptotic cell loss during DM through the epidermal growth factor receptor (133). mTOR can prevent apoptosis and limit insulin resistance as well as vascular thrombosis in patients with metabolic syndrome (223). Through mTOR activation, pathways associated with apoptosis and atherosclerosis also can be blocked (224).

Furthermore, control of mTOR is seen as a vital component to other strategies that may be effective to treat DM and its complications. For example, erythropoietin (EPO), a cytokine and an investigational therapeutic strategy for DM (12, 225), targets multiple cellular signal transduction pathways in the body (226, 227) and relies upon mTOR for cytoprotection (2, 32, 42, 199, 228). EPO uses mTOR to increase cell survival during oxygen-glucose deprivation (195, 229), prevent cell injury during β-amyloid exposure (230), modulate bone homeostasis (231), improve cognitive function sepsis-associated encephalopathy (232), promote retinal progenitor cell survival during oxidant stress (233), prevent retinal degeneration in models of polycystic kidney disease (62), and foster the neuronal phenotype of adult neuronal precursor cells (234). During abnormalities in cellular metabolism, EPO facilitates wound healing during DM (50), attenuates AGE-induced toxicity (235), protects endothelial cell survival during experimental models of DM (66, 67), maintains cellular mitochondrial function and energy metabolism (70), limits high glucose-induced oxidative stress in renal tubular cells (138), and reduces the detrimental effects of obesity in animal models (14).

Agents that are effective in controlling DM rely also upon mTOR and the modulation of autophagy to offer cytoprotection. Metformin, a drug used to control hyperglycemia in DM, blocks mTOR activity and promotes autophagy. Metformin protects against endothelial cell

senescence (25), limits androgen up-regulation during prostate cancer through mTOR inhibition (236), and protects against neuronal apoptotic cell death (237). Metformin through pathways that activate AMPK limits cell loss during hypoxia through increased AMPK activity (238), prevents cardiomyopathy in experimental models of DM (239), enhances cardiomyocyte cell survival (34), and reduces cortical infarction during cerebral ischemia (240). Although AMPK under some conditions may provide cellular protection by limiting oxidative stress that can lead to vascular hypertension (95), increasing cell survival during hypoxia (238), and promoting autophagy that may resolve memory impairment (241), AMPK activity as previously noted also may have detrimental effects. In some studies examining cell survival, AMPK activity may foster neuroinflammation (242), lead to aberrant Aβ stress (243) and Aβ toxicity (180), and result in cardiac dysfunction (31) and cardiac tissue hypertrophy (244).

6. SIRT1 and DM

SIRT1, also known as NAD-dependent deacetylase sirtuin-1, has become a key component for the development of therapies directed against DM (4, 10, 186, 245) (Fig. 1). In addition to pathways previously described for WISP1, SIRT1 also employs signal transduction pathways of mTOR to govern cellular survival and metabolism. SIRT1, a histone deacetylase, is one of seven mammalian homologues of the yeast silent information regulator-2 (Sir2) that also oversee post-translational changes of proteins involved with cellular proliferation, survival, and senescence (25, 105, 193, 245). SIRT1 is dependent upon NAD^+ as a substrate (54, 186, 246, 247). Through the salvage pathway of NAD^+ synthesis, nicotinamide phosphoribosyltransferase (NAMPT) catalyzes the conversion of nicotinamide to nicotinamide mononucleotide (53). Nicotinamide mononucleotide is converted to NAD^+ by the nicotinamide/nicotinic acid mononucleotide adenylyltransferase (NMNAT) enzyme family (248). NAMPT activity not only increases cellular NAD levels, but also increases the activity of SIRT1 transcription.

SIRT1 activity also is overseen by NMNAT, mammalian forkhead transcription factors, and AMPK (186, 249–251). NMNAT modulates the deacetylating activity of SIRT1. Mammalian forkhead transcription factors bind to the SIRT1 promoter region that contains a cluster of five putative core binding repeat motifs (IRS-1) and a forkhead-like consensus-binding site (FKHD-L) (127). This allows forkhead transcription factors, such as FoxO1, to control SIRT1 transcription and increase SIRT1 expression (252). AMPK that phosphorylates TSC2 and inhibits mTORC1 activity (21, 199) can increase the cellular NAD^+/NADH ratio leading to the deacetylation of downstream SIRT1 targets that include the peroxisome proliferator-activated receptor-gamma coactivator 1 (PGC-1α), FoxO1 (37), and FoxO3a (253). AMPK also can increase NAMPT during glucose restriction that results in increased NAD^+ and decreased levels of nicotinamide (254), an inhibitor of SIRT1 (3). SIRT1 activators, such as resveratrol, also can activate AMPK through SIRT1 dependent and independent mechanisms (253, 255). Importantly, the level of SIRT1 activity can yield significant consequences for cellular protection. Insufficient SIRT1 activity can be detrimental for vascular cell survival (105, 193, 256), protection against cardiovascular disease (85), and prevention of neuronal injury (174, 257, 258). However, a reduction in

SIRT1 activity also may be required to promote cellular survival in systems involving trophic factors such as as insulin growth factor-1 (259).

Cellular survival through SIRT1 is closely regulated through apoptotic and autophagic pathways. SIRT1 can control the early phases of apoptotic cell death by preventing the externalization of membrane PS exposure (105, 131, 193, 260). In the presence of tumor necrosis factor-α (TNF-α), SIRT1 can protect endothelial progenitor cells (261) and enhance skeletal myoblast survival (262). SIRT1 also can limit neuronal apoptosis in models of traumatic brain injury (263). Loss of SIRT1 in mouse cochlear neurons and in the auditory cortex is associated with hearing loss (264) and loss of SIRT1 activity in human mesenchymal stem cells results in a reduced proliferation rate with increased apoptosis (265). In addition, decreased levels of SIRT1 can occur in smokers and chronic obstructive disease patients that leads to endothelial progenitor cell dysfunction with apoptotic cell death (266). Decreased levels of SIRT1 activity can be the result of apoptotic pathways associated with p38 (267) and c-Jun N-terminal kinase -1 (JNK1) (46) as well as caspase degradation of SIRT1 (268) that can then lead to further activation of caspases (268, 269). As previously described, pathways such as WISP1 prevent SIRT1 degradation and block caspase activation that would otherwise lead to the degradation of SIRT1 (174, 270–272).

SIRT1 also is dependent upon the induction of autophagy to foster cellular survival. For example, SIRT1 activity that promotes autophagy is necessary for the protection of chondrocytes during oxidative stress, since knockdown of the forkhead transcription factors FoxO1 and FoxO3 lead to loss of SIRT1 activity, reduced autophagic related proteins, and subsequent cell death (92). In models of cognitive loss that employ chronic intermittent hypoxia hypercapnia exposure, SIRT1 activation is able to limit apoptotic cell injury and improve cognition through the induction of autophagy (273). During pathways that are associated with cellular metabolism, SIRT1 promotes autophagy in mitochondria (274) that may be required to maintain a healthy mitochondrial pool (275). SIRT1 up-regulation in conjunction with AMPK activation leads to autophagy that is necessary for cellular protection in endothelial cells exposed to oxidized low density lipoproteins that can lead to atherosclerosis (251). These studies that support a protective role for SIRT1 with autophagy and AMPK activation suggest an inverse relationship with mTOR (4). SIRT1 blocks mTOR activity and promotes autophagy to preserve the integrity of embryonic stem cells during oxidant stress (190). SIRT1 also inhibits mTOR signaling to promote neuronal growth (276) and assist with mesangial cell proliferation during high glucose exposure (277). Yet, it should be noted that not all cases of cytoprotection with SIRT1 required induction of autophagy as well as potential mTOR inhibition. In pulmonary models of oxidative stress such as the exposure to cigarette smoke in bronchial epithelial cells, SIRT1 blocks cell injury through the inhibition of of autophagy (187, 278).

Activation of SIRT1 in mature and differentiated cells during DM is in most instances cytoprotective and can avert insulin resistance. SIRT1 activation activation has been shown to increase lifespan in higher organisms such as Drosophila and protect cells from oxidative stress (279, 280). The presence of SIRT1 appears vital for the prevention of insulin resistance. Loss of SIRT1 can result in insulin resistance and excessive hepatic lipid accumulation (44). Gene deletion or inhibition of SIRT1 can alter insulin signaling by

interfering with insulin stimulated insulin receptor phosphorylation and glycogen synthase (281). Over-expression of SIRT1 can decrease hepatic steatosis and improve insulin sensitivity that leads to improved glucose homeostasis (48). In addition, SIRT1 also is utilized by the cytokine EPO to block cell injury during DM. EPO can increase endogenous cellular SIRT1 activity and foster the subcellular trafficking of SIRT1 to the nucleus to result in endothelial cell protection during oxidative stress (193). SIRT1 also is one component that allows EPO to maintain adipose cell energy homeostasis and protect against metabolic disorders such as DM (192).

SIRT1 may avert insulin resistance through a number of mechanisms that involve fat mobilization (44), mTOR signaling (282), as well as modulation of inflammation (101). SIRT1 also can increase insulin signaling in insulin-sensitive organs through pathways that involve Akt and PI 3-K (105, 131, 193, 258, 283, 284) as well as stimulate glucose-dependent insulin secretion from pancreatic β cells by repressing UCP2 (285). Regulation of insulin sensitivity by SIRT1 may require AMPK. Endothelial cell protection from oxidized low-density lipoproteins has been shown to involve SIRT1 as well as AMPK activation (205, 251). Interestingly, SIRT1 activation with AMPK also may be necessary to protect against spatial memory impairment in combined experimental models of DM and Alzheimer's disease, since these studies demonstrate a loss of SIRT1 and AMPK activities that lead to cognitive loss, oxidative stress, and neuronal cell apoptosis (286).

In addition to mature and differentiated cells, SIRT1 also prevents cell injury in stem cells that may be important for treatments related to DM. Recent studies have suggested that stem cell strategies may be effective for at least treating and maintaining glucose homeostasis during DM in animal models (287, 288). SIRT1 has been shown to be necessary to modulate autophagic flux (289) and for the transition of muscle stem cells from a quiescence state to an active state through the induction of autophagy (290). SIRT1 blocks apoptotic cell injury during oxidative stress through the induction of autophagy in endothelial progenitor cells (291). In the cardiovascular system, increased SIRT1 expression enhances the survival of cardiomyoblasts (292). SIRT1 prevents senescence and impaired differentiation in endothelial progenitor cells (293). Mesenchymal stem cells that are subjected to SIRT1 over-expression show increased blood vessel density in the area of cardiac infarcts, reduced cardiac remodeling, and improved cardiac performance in rodent models (294). SIRT1 also may assist aged stem cells that are senescent to foster repair. Aged mesenchymal stem cells that were subjected to pre-conditioning with glucose depletion demonstrated increased expression of SIRT1 in addition to other proliferative entities such as growth factors to lead to improved cardiac performance (295). Other work demonstrates that SIRT1 is necessary for endothelial progenitor cell mobilization and vascular repair during DM in mice (191). In rodent models of DM, SIRT1 can preserve angiogenesis derived from bone marrow-derived early outgrowth cells (296). In addition, patients with Type 2 DM show a down-regulation of endothelial progenitor cells that has been associated with decreased SIRT1 protein levels (297).

However, SIRT1 activation may require a level of modulation since in some systems of the body, decreased SIRT1 activity is necessary for proper stem cell development. In the nervous system, loss of SIRT1 expression with the induction of heat shock protein -70

(HSP70) is required to promote neural differentiation, maturation of embryonic cortical neurons (298), and the differentiation of human embryonic stem cells into motoneurons (299). SIRT1 also is considered a negative regulator of subventricular zone and hippocampal neural precursors in murine animal models, since knockdown of SIRT1 does not eliminate neural precursor numbers but increases the production of neurons in the subventricular zone and the hippocampus (300). In mouse neural stem cells, neuronal differentiation can be driven through the microRNA miR-34a that leads to decreased SIRT1 expression and DNA-binding of p53 (301). Yet, a level of SIRT1 activity appears to be required for different cell types, since in studies with neuronal differentiation, increased expression of SIRT1 enhanced the astrocytic subpopulation of cells that are necessary to support neuronal cell populations (301).

7. Future Considerations

DM affects a significantly greater portion of the world's population each year with many additional individuals remaining undiagnosed. Risk factors such as obesity and concurrent disorders with DM that can involve the cardiovascular systems, renal system, and the nervous system ultimately lead to significant death and disability with staggering healthcare costs consuming large portions of the GDP for many countries. Current therapies for both achieving glucose homeostasis during DM and averting the complications of DM are limited and require the development of novel strategies that can address oxidant stress pathways to regulate programmed cell death through both apoptosis and autophagy. WISP1, a CCN family member, drives cellular proliferation and survival through mechanisms that oversee PI 3-K, Akt, SIRT1, and mTOR that ultimately can limit insulin resistance, lead to stem cell regeneration of injured tissues, and enhance cellular protection through modulation of apoptosis and autophagy during DM (Fig. 2). Independently, mTOR can block apoptotic pathways to enhance pancreatic β-cell proliferation, resolve insulin resistance, inhibit pathways tied to atherosclerosis, and avert oxidative stress mediated cellular injury through agents that involve cytokines such as EPO and oral hypoglycemics such as metformin. In some pathways with mTOR, it is the inhibition of mTOR that is required for cytoprotective pathways of autophagy to proceed. Although SIRT1 employs "anti-apoptotic" mechanisms to increase cell survival and preserve insulin signaling during oxidant stress exposure, SIRT1 also appears at times to have an inverse relationship with mTOR to block mTOR activation and foster autophagy for the preservation of cellular energy organelles involving mitochondria, the promotion of stem cell proliferation, and the prevention of apoptosis. Pathways linking WISP1, mTOR, and SIRT1 with apoptosis and autophagy involve AMPK, a pathway intimately tied to glucose homeostasis that can prevent tissue ischemia, insulin resistance, cognitive loss, and cell death. Targeting WISP1, mTOR, and SIRT1 for the treatment of glucose control in DM as well as the complications of this disease opens exciting prospects to eventually limit the devastating and growing impact DM has on the world's population. Yet, it is imperative that future work addresses the fine biological control WISP1, mTOR, and SIRT1 hold over metabolism to precisely modulate cellular signaling, since these pathways under specific conditions can yield unwanted clinical outcomes that involve induction of fibrotic tissue injury (161), tumorigenesis (302–305), inflammation (242), progression of neurodegenerative disorders (180, 243), cardiac

dysfunction (31), loss of neuronal embryonic stem cells that may limit reparative processes in the nervous system (298, 300), and apoptosis in pancreatic islet cells (206).

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WISP1, mTOR, and SIRT1 HIGHLIGHTS IN DIABETES MELLITUS

1. WISP1 is a target of the *wingless* pathway Wnt1 and a matricellular protein that affects oxidative stress, programmed cell death, extracellular matrix production, cellular migration, and mitosis.
2. WISP1 can influence induced pluripotent stem cell reprogramming, differentially regulate adipose-derived stem cell differentiation, foster pancreatic regeneration, and may play a role in vascular repair and insulin resistance with obesity.
3. mTOR is a 289-kDa serine/threonine protein kinase, an essential component of the protein complexes mTORC1 and mTORC2, and blocks insulin resistance, prevents apoptotic cell injury that can lead to pancreatic β- cell loss, leads to cytoprotection and maintains cellular energy metabolism through cytokines such as EPO, and fosters pancreatic β- cell proliferation.
4. Through pathways that lead to the induction of autophagy that limits mTOR activation, metformin as well as AMPK can prevent myocardial ischemia is models of DM, block lipid accumulation, reduce oxidative stress, and limit insulin resistance.
5. SIRT1, a histone deacetylase, oversees post-translational changes of proteins involved with cellular proliferation, survival, and senescence and can increase lifespan in higher organisms, enhance insulin signaling, maintain adipose cell energy homeostasis, and block endothelial cell apoptosis during oxidative stress.
6. SIRT1 modulates autophagic flux, is necessary for endothelial progenitor cell mobilization and vascular repair during DM, enhances the survival of cardiomyoblasts, improves cardiac performance, and modulates fat mobilization.

Figure 1.
Topical Highlights for WISP1, mTOR, and SIRT1 in Diabetes Mellitus

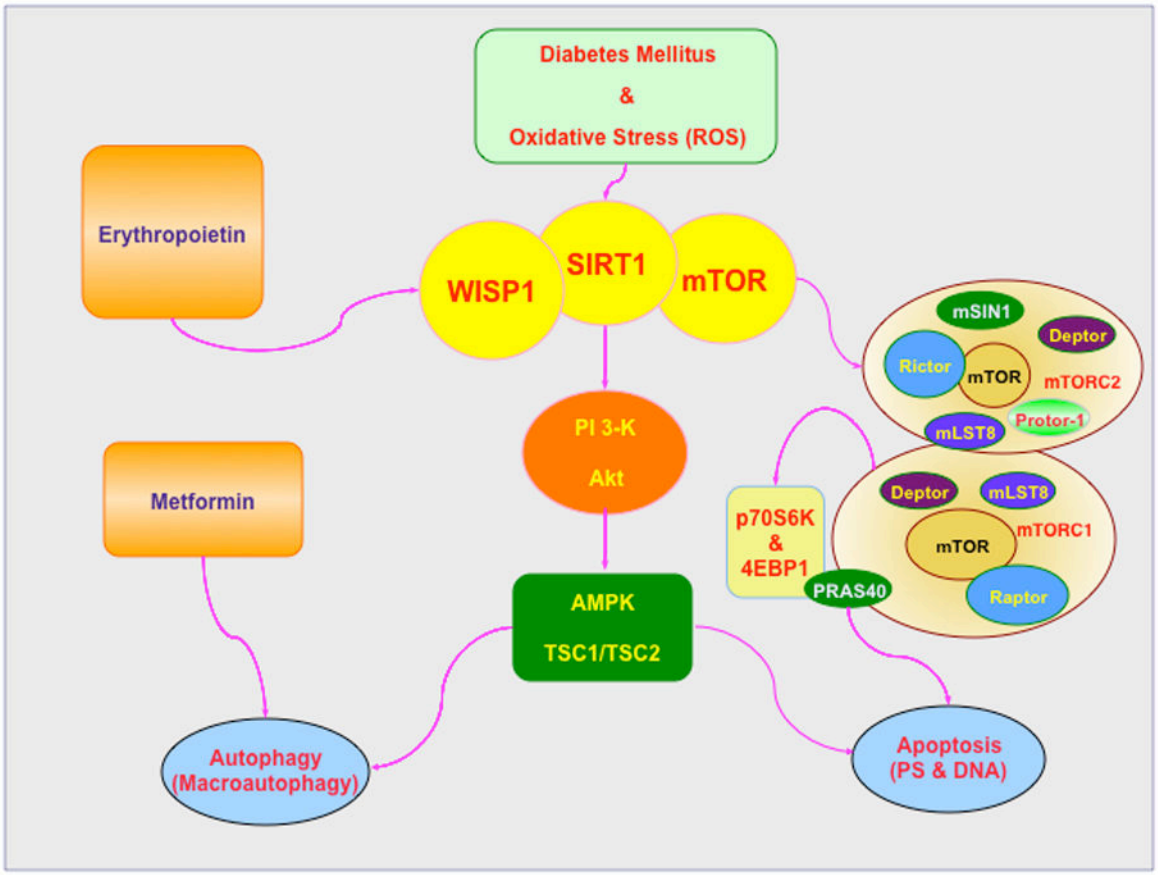

Figure 2. Apoptosis and Autophagy Pathways for WISP1, mTOR, and SIRT1 During Oxidative Stress and Diabetes Mellitus

Oxidative stress is an important determinant of cell injury in diabetes mellitus (DM) and leads to the generation of reactive oxygen species (ROS) that can significantly affect cellular metabolism. Ultimately, DM through oxidative stress can lead to apoptotic cell injury that consists of an early phase involving the loss of plasma membrane lipid phosphatidylserine (PS) asymmetry and a later phase that leads to genomic DNA degradation. During autophagy in DM, macroautophagy plays a principal role and involves the sequestration of cytoplasmic proteins into autophagosomes that fuse with lysosomes for degradation and recycling for future cellular processes. WISP1, mTOR, and SIRT1 through shared as well as independent pathways can oversee phosphoinositide 3 –kinase (PI 3-K), protein kinase B (Akt), AMP activated protein kinase (AMPK), and the the hamartin (tuberous sclerosis 1)/ tuberin (tuberous sclerosis 2) (TSC1/TSC2) complex to control multiple biological outcomes that include insulin resistance, stem cell proliferation, glucose homeostasis, and cell survival. The cytokine erythropoietin (EPO) uses *wingless* pathways of Wnt1, SIRT1, and mTOR to help maintain mitochondrial function and vascular survival during DM. Metformin, a hypoglycemic agent, limits mTOR activity and promotes autophagy to not only regulate serum glucose, but also limit cellular injury during DM. mTOR is an essential component of the protein complexes mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2). Activation of mTOR leads to down stream signaling with the cytoprotective pathways of p70 ribosomal S6 kinase (p70S6K) and the eukaryotic initiation factor 4E-

binding protein 1 (4EBP1). In contrast, mTOR activity can be blocked by the proline rich Akt substrate 40 kDa (PRAS40) as well as by AMPK through the TSC1/TSC2 complex.