Novel applications of trophic factors, Wnt and WISP for neuronal repair and regeneration in metabolic disease

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Abstract

Diabetes mellitus affects almost 350 million individuals throughout the globe resulting in significant morbidity and mortality. Of further concern is the growing population of individuals that remain undiagnosed but are susceptible to the detrimental outcomes of this disorder. Diabetes mellitus leads to multiple complications in the central and peripheral nervous systems that include cognitive impairment, retinal disease, neuropsychiatric disease, cerebral ischemia, and peripheral nerve degeneration. Although multiple strategies are being considered, novel targeting of trophic factors, Wnt signaling, Wnt1 inducible signaling pathway protein 1, and stem cell tissue regeneration are considered to be exciting prospects to overcome the cellular mechanisms that lead to neuronal injury in diabetes mellitus involving oxidative stress, apoptosis, and autophagy. Pathways that involve insulin-like growth factor-1, fibroblast growth factor, epidermal growth factor, and erythropoietin can govern glucose homeostasis and are intimately tied to Wnt signaling that involves Wnt1 and Wnt1 inducible signaling pathway protein 1 (CCN4) to foster control over stem cell proliferation, wound repair, cognitive decline, β-cell proliferation, vascular regeneration, and programmed cell death. Ultimately, cellular metabolism through Wnt signaling is driven by primary metabolic pathways of the mechanistic target of rapamycin and AMP activated protein kinase. These pathways offer precise biological control of cellular metabolism, but are exquisitely sensitive to the different components of Wnt signaling. As a result, unexpected clinical outcomes can ensue and therefore demand careful translation of the mechanisms that govern neural repair and regeneration in diabetes mellitus.

Key Words: Alzheimer's disease; AMPK; apoptosis; autophagy; central nervous system; CCN4; EGF; diabetes mellitus; erythropoietin; EPO; FGF; IGF-1; mTOR; neuron; neuropathy; oxidative stress; psychiatric; stem cells; WISP1; Wnt

The Impact of Diabetes Mellitus on the Nervous System

The incidence of diabetes mellitus (DM) is increasing in accordance with the growth of obesity in the world's population (Maiese et al., 2011a, 2013c; Rutter et al., 2012; Jia et al., 2014; Xu et al., 2014a). Obesity can lead to DM (Lim et al., 2014) as well as independently result in metabolic dysfunction. Excess body fat can precipitate pancreatic β cell injury (Shao et al., 2013), cellular inflammation (Essser et al., 2014), impaired growth factor release (Maiese et al., 2005b, 2012a; White, 2014; Zhang et al., 2014c), changes in protein tyrosine phosphatase signaling (Chong and Maiese, 2007; Xu et al., 2014a), oxidative stress (Maiese et al., 2013c; Liu et al., 2014), and insulin resistance (Maiese et al., 2007a; Caron et al., 2014; Essser et al., 2014). With the significant increases in DM and obesity, the World Health Organization estimates that DM will be the seventh leading cause of

death in the year 2030 (World Health Organization, 2011). Worldwide, approximately 347 million individuals suffer form DM. In the United States (US) alone, 21 million individuals are diagnosed with DM. Yet, of equal concern is that an estimated additional 8 million individuals presently remain undiagnosed with DM but remain susceptible to the ill effects of this disease (Centers for Disease Control and Prevention, 2014). It is believed that DM costs US employers $69 billion in reduced productivity and another $176 billion for direct medical costs. This represents a significant cost for the country especially with the Centers for Medicare and Medicaid Services reporting that the US spends 2.8 trillion on healthcare that equals $8,915 per person and 17.2 percent of the Gross Domestic Product.

Although some overlap exists, DM can be divided into either non-insulin dependent (Type 1) DM or insulin dependent (Type 2) DM (Maiese et al., 2010a, 2013b). In approximately 90% of individuals with DM, Type 2 DM is present

and usually occurs in individuals over the age of 40. It presents with a progressive deterioration of glucose tolerance with early β-cell compensation (Maiese et al., 2007b, 2013c). Loss of insulin secretion can result from impaired β-cell function, prolonged exposure to free fatty acids and hyperglycemia, and the absence of inhibitory feedback through plasma glucagon levels. Type 1 DM occurs in the remaining 10% of patients with DM and it is considered to be the result of an autoimmune disorder associated with the alleles of the human leukocyte antigen class II genes within the major histocompatibility complex (Maiese et al., 2007b). Loss of insulin production and homeostasis occurs as a result of the destruction of pancreatic β-cells with inflammatory infiltration of the islets of Langerhans. Approximately 90% of patients with Type 1 DM have increased titers of autoantibodies (Type 1A DM), but the remaining 10% of Type 1 DM individuals do not have serum autoantibodies. These individuals have maturity-onset diabetes of the young (MODY) that can be the result of β-cell dysfunction with autosomal-dominant inheritance (Type IB DM). Type 1 and Type 2 DM are not completely independent entities since almost 10% of individuals with Type 2 DM may have elevated serum autoantibodies similar to Type 1 DM. In addition, insulin resistance also may be a component of Type 1 DM in some patients.

DM affects all components of the central and peripheral nervous systems. For example, DM can foster retinal disease (Tang et al., 2011; Fu et al., 2012; Busch et al., 2014), injury to the neuroglialvascular unit (Busch et al., 2014), angiogenesis impairment (Chen et al., 2012), endothelial cell demise (Chong et al., 2007; Hou et al., 2010a; Chong et al., 2011b; Schaffer et al., 2012; Liu et al., 2013c; Wang et al., 2014; Zhang et al., 2014c), endothelial cell senescence (Arunachalam et al., 2014), dysfunctional maintenance and mobilization of endothelial progenitor cells (Barthelmes et al., 2014; Kim et al., 2014), and peripheral nerve disorders (Schmeichel et al., 2003; Gomes and Negrato, 2014). Although it is estimated that 60–70% of individuals with DM can develop some degree of peripheral neuropathy, the incidence of disorders such as peripheral neuropathy can be difficult to assess since the course of the disease may occur over several years, initial progression of the disease may be sub-clinical, and improved control of DM may lead to correction of prior clinical deficits. DM also can result in memory loss (Zhao et al., 2013; Mao et al., 2014; Du et al., 2015), neuropsychiatric disorders (Aksu et al., 2012; Reagan, 2012), stroke (Jiang et al., 2014), and impairment of neuronal longevity (White, 2014). Furthermore, complications of DM such as insulin resistance and dementia has been reported in patients with Alzheimer's disease (Maiese et al., 2007b; Sonnen et al., 2009), indicating that some neurodegenerative disorders may be the result of impaired cellular metabolism similar to that which occurs during DM (Kapogiannis et al., 2014).

Diabetes Mellitus, Oxidative Stress, and Programmed Cell Death

The generation of reactive oxygen species (ROS) leading to the induction of oxidative stress can be a critical determinant of neuronal and vascular cell injury during DM (Yang et al., 2011b; Bagul and Banerjee, 2013; Liu et al., 2013b; Maiese et al., 2013b, c; Peng et al., 2013; Weinberg et al., 2014; Xu et al., 2014b). ROS can alter cellular metabolic pathways (Maiese et al., 2010a, 2011a; Fu et al., 2012; Gomes and Negrato, 2014; Xu et al., 2014b) and influence epigenetic pathways (Maiese et al., 2008b; Fraineau et al., 2014; Jenwitheesuk et al., 2014; Xin et al., 2015) with subsequent nervous system deficits that lead to cognitive loss (Chong et al., 2005a; Kim et al., 2015; Wright and Harding, 2015), post-traumatic injury (Harish et al., 2015), and stroke (Chong et al., 2005b; Peng et al., 2015). ROS include superoxide free radicals, nitric oxide, hydrogen peroxide, and singlet oxygen that result in mitochondrial dysfunction, DNA destruction, cell injury, and protein misfolding (Chong et al., 2005b; Maiese et al., 2013b; Asaithambi et al., 2014; Chen et al., 2014a; Palma et al., 2014; Zeldich et al., 2014). Protective pathways within the body and nervous system can serve to limit the deleterious effects of ROS and oxidative stress. These include vitamins such as B, C, D, and K (Maiese et al., 2009; Bowes Rickman et al., 2013; Miret and Munne-Bosch, 2014; Xu et al., 2014b; Yousef and Mohamed, 2015) as well as catalase, glutathione peroxidase, and superoxide dismutase (Li et al., 2012; Muley et al., 2012; Maiese et al., 2013b; Vishwas et al., 2013; Akasaki et al., 2014; Gezginci-Oktayoglu et al., 2014; Mao et al., 2014; Moghaddasi et al., 2014; Palma et al., 2014; Srivastava and Shivanandappa, 2014; Zhou et al., 2014b).

Patients with Type 2 DM have serum markers of oxidative stress with ischemia-modified albumin (Kurban et al., 2011). Interestingly, brief periods as well as chronic exposure of hyperglycemia that can occur during DM can lead to ROS (Yano et al., 2004; Monnier et al., 2006). Formation of ROS and activation of caspases (Weinberg et al., 2014) can occur through advanced glycation end products (AGEs), entities that lead to complications in DM (Maiese, 2008; Chong and Maiese, 2012). In addition, glucolipotoxicity caused by elevated plasma glucose and high lipid levels promotes oxidative stress with cytochrome c release, caspase activation, and apoptosis in pancreatic β-cells (Liu et al., 2012b). High fat diets (Ribeiro et al., 2009) and free fatty acids also have been shown to result in ROS generation, lead to mitochondrial DNA damage, and result in pancreatic β-cell dysfunction (Rachek et al., 2006). During oxidative stress with DM, opening of the mitochondrial membrane permeability transition pore occurs to promote cytochrome c release and caspase activity (Hou et al., 2010a, b; Chong et al., 2011b; Tang et al., 2011; Cardoso et al., 2012; Du et al., 2015; Mao et al., 2014). Alterations in uncoupling proteins (UCPs) also occur that influence cell survival during DM (Maiese et al., 2007a; Liu et al., 2013b; Zhang et al., 2014b). Uncoupling of respiration by UCPs can alter ATP synthesis, fatty acid release, and glucose oxidation. Ultimately, mitochondrial dysfunction and UCP activity can then be followed by programmed cell death with apoptosis and autophagy (Fu et al., 2012).

Apoptosis (Maiese et al., 2010b; Damasceno et al., 2013; Gomes and Negrato, 2014; Wang et al., 2014; Xu et al.,

2014b) and autophagy (Maiese et al., 2012b, 2013b; Yamada and Singh, 2012; Jia et al., 2014) are pathways of programmed cell death that play significant roles in controlling cell survival during DM and oxidative stress. With apoptosis, there exists an early phase that consists of the loss of plasma membrane lipid phosphatidylserine asymmetry that can identify cells for disposal by microglia in the nervous system (Schutters and Reutelingsperger, 2010; Wei et al., 2013; Williams and Dexter, 2014). A later phase in apoptosis results in cell death with DNA degradation (Chong et al., 2005b, 2006; Favaloro et al., 2012; Folch et al., 2012; Shao et al., 2013; Nguyen et al., 2014). During DM, apoptosis results in the death of neurons (Das et al., 2011; Aksu et al., 2012; Kimura et al., 2013; Mao et al., 2014), pancreatic β-cell loss (Deng et al., 2009; Choi et al., 2010; Miao et al., 2013), and endothelial cell destruction (Chong et al., 2007; Hou et al., 2010b; Hamed et al., 2011; Chen et al., 2012; Arunachalam et al., 2014).

Autophagy has three categories that permit cells to recycle cytoplasmic components and eliminate dysfunctional organelles for tissue remodeling (Maiese et al., 2012b; Cai and Yan, 2013; Chen et al., 2014b, c; Nakka et al., 2014). Of the three categories for autophagy, microautophagy employs the invagination of the lysosomal membrane for the sequestration and digestion of cytoplasmic components (Maiese et al., 2012b). In chaperone-mediated autophagy, cytosolic chaperones transport cytoplasmic components across lysosomal membranes. The most prevalent category of autophagy is macroautophagy that consists of the sequestration of cytoplasmic proteins and organelles into autophagosomes. These autophagosomes then combine with lysosomes for degradation and are subsequently recycled for future cellular processes. Autophagy has both a beneficial and detrimental side during DM (Chong et al., 2012c; Maiese et al., 2013c; Chen et al., 2014b; Min et al., 2014; Nakka et al., 2014). Exercise in mice has been shown to initiate autophagy and regulate glucose homeostasis (He et al., 2012). In addition, autophagy can improve insulin sensitivity during high fat diets in mice (Liu et al., 2014). Without autophagy, obesity may progression to DM, since experimental studies illustrate that autophagy haploinsufficiency in murine animal models of obesity can lead to increased insulin resistance with elevated lipids and inflammation (Lim et al., 2014). Autophagy also may be necessary to eliminate misfolded proteins and non-functioning mitochondria to prevent β-cell dysfunction and the onset of DM (Liu et al., 2013d). Yet, as noted, autophagy can play a detrimental role in DM. Although apoptosis may be a greater contributor to neuronal death than autophagy (Wang et al., 2012b), autophagy can impair endothelial progenitor cells, lead to mitochondrial oxidative stress, and prevent the formation of new blood vessels during elevated glucose exposure (Kim et al., 2014). AGEs also result in the induction of autophagy and vascular smooth muscle proliferation that can lead to atherosclerosis (Hu et al., 2012) and cardiomyopathy (Lee et al., 2012b). Furthermore, increased activation of autophagy can lead to loss of cardiac and liver tissue in diabetic rats during attempts to achieve glycemic control

through diet modification (Lee et al., 2014).

Targeting Trophic Factors for DM in the Nervous System

For the nervous system, a number of avenues are being pursued to treat the complications of DM and oxidative stress. These include the modulation of sirtuins (Hou et al., 2010b; Maiese et al., 2011b; Chong et al., 2012a; Halperin-Sheinfeld et al., 2012; Shao et al., 2013; Arunachalam et al., 2014; Moroz et al., 2014), metabotropic receptors (Lin and Maiese, 2001; Maiese et al., 2007b, 2008c; Domin et al., 2014; Jantas et al., 2014; Domin et al., 2015), nicotinamide adenine dinucleotide (NAD^+) precursors (Maiese et al., 2009, 2011a; Zhou et al., 2009; John et al., 2012; Carneiro et al., 2013; Ghasemi et al., 2014), protein tyrosine phosphatases (Chong and Maiese, 2007; Chen et al., 2012; Xu et al., 2014a; Geldman and Pallen, 2015), anti-oxidant therapies (Schaffer et al., 2012; Bagul and Banerjee, 2013; Gomes and Negrato, 2014; Xu et al., 2014b; Yousef and Mohamed, 2015), and trophic factors (Maiese et al., 2005b, 2008d, 2012a; Barthelmes et al., 2014; Hamed et al., 2014; Wang et al., 2014; White, 2014; Zhang et al., 2014c).

Growth factors are of particular interest since complications of DM and oxidative stress may be exacerbated during the loss of trophic factors (**Figure 1**). In experimental animal models of DM, oxidative stress may lead to reduced expression of insulin-like growth factor-1 (IGF-1), increased apoptosis of prefrontal cortex neurons, and subsequent anxiety (Aksu et al., 2012). In addition, insulin producing cells derived from stem cells may require the specific presence of fibroblast growth factor (FGF) and epidermal growth factor (EGF) (Czubak et al., 2014), growth factors that have been demonstrated to block neuronal injury during oxidative stress (Maiese et al., 1993). EGF also promotes the neuroprotective effects of glucagon-like peptide-1 against neuronal cell apoptosis in cell culture models of DM (Kimura et al., 2013) and FGF may block vascular disease during DM (Zhang et al., 2013). Erythropoietin (EPO) is another trophic factor of interest for DM since it can prevent retinal and photoreceptor injury from insults such as excessive light (Colella et al., 2011), oxidative stress (Shen et al., 2014) and DM (Busch et al., 2014). EPO can have multiple beneficial effects and lead to reduced blood glucose levels in animal models of DM and obesity (Katz et al., 2010), attenuate oxidative stress and apoptosis in Schwann cells mediated by AGEs (Yu et al., 2015), and protect endothelial cells during experimental models of DM (Chong et al., 2007, 2011b). Furthermore, EPO can limit high glucose-induced oxidative stress in renal tubular cells (Dang et al., 2010), control the detrimental effects of obesity in animal models (Zhang et al., 2014c), promote wound healing during DM (Hamed et al., 2014), and foster cellular mitochondrial function and energy metabolism (Wang et al., 2014). Through improvement of vascular perfusion by EPO (Kang et al., 2014), EPO may ultimately lead to cognitive repair (Hralova et al., 2013), reduce seizure occurrence (Castaneda-Arellano et al., 2014), and block peripheral nerve injury during DM (Yu et al., 2014).

Cellular Pathways of Wingless, the CCN Family, and Stem Cells

However, growth factors such as EPO rely upon multiple cellular pathways to exert cellular protection (Chong et al., 2002, 2003, 2012b; Maiese et al., 2008a; Chamorro et al., 2013; Kwon et al., 2014; Ma et al., 2014; Parvin et al., 2014; Schafer et al., 2014; Zhang et al., 2015). In regards to DM and oxidative stress, EPO relies upon the wingless pathway of Wnt proteins (**Figure 1**). Wnt proteins are cysteine-rich glycosylated proteins that control multiple processes involving neuronal development, angiogenesis, immunity, tumorigenesis, fibrosis, and stem cell proliferation (Li et al., 2006; Maiese et al., 2008e; Wexler et al., 2011; Zeljko et al., 2011; Heo et al., 2013; Berwick and Harvey, 2014; Thorfve et al., 2014). In the nervous system, Wnt signaling may be instrumental in the pathogenesis of disorders such as Parkinson's disease (Marchetti et al., 2013; Berwick and Harvey, 2014), protect against neuronal mitochondrial injury and cerebral ischemia (Chong et al., 2010; Xing et al., 2012, 2014), limit spinal cord injury (Gonzalez-Fernandez et al., 2013), maintain microglial and macrophage integrity and function (Shang et al., 2010; Wang et al., 2015), and serve as an anti-depressant (Pilar-Cuellar et al., 2013). Through pathways that involve the Wnt1 protein, EPO blocks cerebral endothelial cell injury in models of experimental diabetes (Chong et al., 2007). EPO prevents the loss of Wnt1 expression that would occur in the absence of EPO during elevated glucose. In studies that block Wnt1 with a Wnt1 antibody, EPO protection is neutralized, indicating that Wnt1 is vital for the protection of EPO during elevated glucose exposure such as DM (Chong et al., 2007). EPO also may require Wnt signaling for the preservation of mesenchymal stem cells (Danielyan et al., 2009), to control "pro-apoptotic" forkhead transcription factors in DM (Chong et al., 2011b), foster the maintenance of immune cells of the nervous system during oxidative stress (Shang et al., 2011), and block β-amyloid (Aβ) toxicity in microglia of the brain (Shang et al., 2012b).

Independent of EPO, Wnt1 and Wnt signaling can block autophagy (Wang et al., 2012b; Fu et al., 2014; Geng et al., 2014; Ortiz-Masia et al., 2014) and apoptotic endothelial cell injury during elevated glucose exposure (Chong et al., 2007) (**Figure 1**). Wnt signaling also promotes human β-cell proliferation (Aly et al., 2013), fosters the repair of diabetic wounds (Sun et al., 2014), impacts the vasculature of the brain (Guo et al., 2012), and prevents cognitive decline during aging and potential concomitant disease such as during DM (Bayod et al., 2014a). Components of the Wnt pathway also have increased expression in the brain during periods of exercise (Bayod et al., 2014b) that may assist against insulin resistance. Given the complexities of the Wnt signaling pathway and the ability of Wnt to promote angiogenesis (Chong et al., 2011a; Cui et al., 2012; Lee et al., 2012a; Maiese, 2014d), it should be noted that Wnt signaling in some cases can potentiate injury such as vascular leakage and inflammation during DM retinopathy (Lee et al., 2012a), promote retinal oxidative stress (Zhou et al., 2011; Liu et al., 2013c), and lead to keratoconus cornea (Iqbal et al., 2013). Furthermore,

Wnt1 and Wnt signaling pathways are proliferative in nature and can result in tumorigenesis. In the nervous system Wnt signaling may lead to malignant glioma development (Liu et al., 2012a; Tu et al., 2013), malignant melanoma (Uzdensky et al., 2013), and metastatic disease (James et al., 2012; Kafka et al., 2014; Klinke, 2014; Knoblich et al., 2014). In addition, growth factors such as EPO with prolonged exposure can have non-beneficial effects such as the proliferation of cancer (Maiese et al., 2005a; Hedley et al., 2011; Zhang et al., 2014a), increased risk during cardiac conditions and hypertension (Palazzuoli et al., 2014), inflammation, and blood-brain barrier injury (Ogunshola et al., 2013).

A downstream target in the Wnt1 pathway is Wnt1 inducible signaling pathway protein 1 (WISP1), a protein that is present in the brain, epithelium, heart, kidney, lung, pancreas, placenta, ovaries, small intestine, and spleen (Maiese, 2014d). WISP1, also known as CCN4, is a member of the six secreted extracellular matrix associated CCN family of proteins that are mediators of skeletal system development, vascular repair, cellular survival, and extracellular matrix growth. The CCN term 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.

Initial studies demonstrated that WISP1 stops p53 mediated DNA damage and apoptosis (Su et al., 2002). Subsequent work with WISP1 further illustrated the ability to prevent apoptosis (Price et al., 2004; Venkatesan et al., 2010; Wang et al., 2013), control caspase activation (Venkatesan et al., 2010; Wang et al., 2012a, 2013), and oversee autophagy (Maiese et al., 2012b; Wang et al., 2012b). For regeneration and/or repair of injury in the nervous system, WISP1 may have a critical role. The expression of WISP1 is increased during oxidative stress in neurons and the presence of WISP1 is necessary for neuronal protection by reducing the expression of the Bim/Bax complex, increasing the expression of Bclx(L)/Bax complex, and blocking cytochrome c release with caspase 3 activation (Wang et al., 2012a). WISP1 also autoregulates its own expression by maintaining the activity of β-catenin and limiting the induction of autophagy (Wang et al., 2012b). In addition, WISP1 can protect neurons by controlling the forkhead transcription factor FoxO3a, a modulator of cellular metabolism and cell survival (Maiese et al., 2008b; Chong et al., 2011b; Uranga et al., 2013; Fong et al., 2014; Safarian et al., 2014; Zeldich et al., 2014). Furthermore, WISP1 promotes the nuclear trafficking and increased activity of the silent mating type information regulation 2 homolog 1 (S. cerevisiae) (SIRT1) which can lead to neuronal protection (Wang et al., 2013) and block apoptotic injury (Hou et al., 2010b; Tanno et al., 2010; Hou et al., 2011).

In regards to DM and the control of cellular metabolism, WISP1 is one of several genes that are over-expressed during pancreatic regeneration, suggesting that WISP1 may oversee stem cell development during DM (Lim et al., 2002) (**Figure 1**). WISP1 can regulate induced pluripotent stem cell reprogramming (Yang et al., 2011a; Jung et al., 2014) and stem cell migration (Lough et al., 2013). Expression of WISP1 also is increased during human adipocyte differentiation (Murahovschi et al., 2014) and may support

THERAPEUTIC CONSIDERATIONS IN METABOLIC DISEASE FOR TROPHIC FACTORS, WNT SIGNALING, AND WISP1

1. Growth factors, such as insulin-like growth factor-1 (IGF-1), fibroblast growth factor (FGF), epidermal growth factor (EGF), and erythropoietin (EPO), can foster insulin production and stem cell development, block oxidative stress, promote glucose homeostasis, and prevent apoptotic cell death in the nervous system.
2. Trophic factors may directly limit excessive serum glucose levels, improve vascular function and energy metabolism, and assist against the detrimental effects of obesity.
3. Wnt signaling, that includes the cysteine-rich glycosylated Wnt proteins, protects against neurodegenerative disorders, controls programmed cell death through apoptosis and autophagy, and is utilized by some trophic factors to prevent neurovascular disease during diabetes mellitus (DM).
4. Wnt signaling leads to human β-cell proliferation, promotes the repair of diabetic wounds, has increased expression in the brain during exercise that may prevent insulin resistance, and inhibits cognitive decline during aging and concomitant disease with DM.
5. Wnt1 inducible signaling pathway protein 1 (WISP1), a downstream target in the Wnt1 pathway, can oversee stem cell development during DM and controls the mechanistic target of rapamycin (mTOR) and AMP activated protein kinase (AMPK) to govern cellular metabolism and promote neuronal viability during DM.
6. Specific and controlled targeting of trophic factors, Wnt signaling, and WISP1 is required since these entities also play a role in vascular leakage, excessive angiogenesis, pancreatic islet cell death, and tumorigenesis.

Figure 1 Therapeutic strategies in metabolic disease with trophic factors, wnt signaling, and WISP1.

vascular regeneration during saphenous vein crush injury (Price et al., 2004). WISP1 fosters vascular smooth muscle proliferation that can assist with tissue repair during injury (Reddy et al., 2011; Liu et al., 2013a), but modulates cellular senescence (Du et al., 2014) and does not promote excessive cellular proliferation in aging vascular cells (Marchand et al., 2011), a component of atherosclerosis. WISP1 expression also is affected by weight change in humans and increases during insulin resistance in glucose-tolerant individuals (Murahovschi et al., 2014), indicating that WISP1 may represent an important reparative process in individuals with DM.

In relation to cellular mechanisms that impact DM, WISP1 employs metabolic pathways that involve the mechanistic target of rapamycin (mTOR) to prevent the injury to the central nervous system (Chong et al., 2012c; Maiese, 2014c). WISP1 through mTOR downstream pathways that modulate the proline rich Akt substrate 40 kDa (PRAS40) (Shang et al., 2012a) and tuberin (tuberous sclerosis 2) TSC2 (Shang et al., 2013) can increases cell survival for microglial cells against oxidative stress and Aβ toxicity. mTOR is closely tied to cellular metabolism (Maiese et al., 2013a, 2014a; Johnson et al., 2015) and independently can prevent apoptotic injury in pancreatic β-cells (Zhou et al., 2014a), lead to pancreatic β-cell proliferation (Miao et al., 2013), inhibit neuronal cell apoptosis during DM through the EGF receptor (Kimura et al., 2013), and limit vascular disease with atherosclerosis (Peng et al., 2014). WISP1 also controls the post-translational phosphorylation of AMP activated protein kinase (AMPK) that is involved in glucose homeostasis (Chong and Maiese, 2012; Maiese et al., 2013c; Kopp et al., 2014; Martinez de Morentin et al., 2014). AMPK regulates the activity of the hamartin (tuberous sclerosis 1)/tuberin (tuberous sclerosis 2) (TSC1/TSC2) complex that is an inhibitor of mTOR Complex 1 (mTORC1) (Maiese, 2014b). The ability of WISP1 to oversee AMPK activity is vital to control cellular metabolism during DM (Martinez de Morentin et al., 2014). WISP1 modulates AMPK activation by differentially decreasing phosphorylation of TSC2 at Ser1387, a target of AMPK, and increasing phosphorylation of TSC2 at Thr1462, a target of protein kinase B (Akt) (Shang et al., 2013). This enables WISP1 to provide a minimal level of TSC2 and AMPK activity to control both cell survival and cell metabolism (Shang

et al., 2013). Under some scenarios, increased AMPK activity can reduce insulin resistance and diminished oxidative stress mediated through the activation of autophagy (Liu et al., 2014). AMPK activation also can result in correcting metabolic parameters of cells (Jessen et al., 2010) and prevent adipocyte differentiation, lipid accumulation, and obesity (Lai et al., 2012). Yet, the degree of AMPK activity remains an important consideration, since in some experimental models of Type 2 DM, AMPK activation promotes apoptotic cell death in pancreatic islet cells (Guan et al., 2014).

However, similar to the pathways of Wnt1, WISP1 is a proliferative agent and may have a role in tumor cell development and proliferation (Maiese, 2014d) (**Figure 1**). Under some circumstances, WISP1 independently may result in cancer growth (Klinke, 2014) and increased combined expression of Wnt1, WISP1, survivin, and cyclin-D1 may be suggestive that these pathways work synergistically to lead to tumorigenesis with the inhibition of apoptosis (Khor et al., 2006). During chronic ethanol consumption, WISP1 is associated with hepatic cell proliferation that may be not only reparative, but also associated with liver cancer (Mercer et al., 2014). WISP1 expression in the nervous system also is increased in neurofibromatosis type 1 tumorigenesis (Pasmant et al., 2010). Variants of WISP1 have been described to be extremely aggressive in promoting cell growth (Tanaka et al., 2003), but non-variant WISP1 expression may block tumor cell invasion, motility, and metastases (Soon et al., 2003). Differential expression of CCN family members in breast cancer also has suggested that WISP1 may function to limit breast cancer growth (Davies et al., 2007) and Notch1 activation that leads to increased WISP1 expression can suppress melanoma growth (Shao et al., 2011). Yet, WISP1 may be able to limit metastatic disease only under certain cellular conditions, since some studies also suggest that WISP1 may promote distant metastatic disease (Ono et al., 2013).

Future Considerations for Promoting Neuronal Protection in DM

DM can lead to significant complications in the central as well as the peripheral nervous systems. Complications can include loss of vision due to retinal disease, impaired cog-

nition with dementia that my involve Alzheimer's disease, destruction of the blood brain barrier that results in ischemic cerebral disease, and peripheral nerve dysfunction. At the cellular level, neuronal cell injury during DM can occur through oxidative stress and the generation of ROS that ultimately lead to apoptosis and autophagy. Although apoptosis usually results in cell death, autophagy under some circumstances can be protective during DM and may control insulin resistance and prevent β-cell dysfunction.

Given the complex cellular processes that can result in neuronal cell injury during metabolic disease, novel targeting with trophic factors, Wnt, WISP1, and the oversight of stem cell proliferation may offer new strategies to prevent the complications of DM in the nervous system. Growth factors such as IGF-1, FGF, EGF, and EPO can modulate glucose homeostasis and prevent neuronal injury during oxidative stress and DM. EPO also employs pathways of Wnt signaling to protect against cerebral endothelial cell injury, block "pro-apoptotic" pathways, and maintain the integrity of immune cells of the nervous system. Independently, Wnt signaling that involves Wnt1 and WISP1 (CCN4) is becoming recognized as a vital neuroprotective component during DM to modulate stem cell proliferation, repair diabetic wounds, reverse cognitive decline, increase human β-cell proliferation, promote vascular regeneration, and control programmed cell death through apoptosis and autophagy. Cellular mechanisms of Wnt and WISP1 govern primary metabolic pathways of mTOR and AMPK. However, it appears that the degree of activation of these biological systems is an important consideration in developing therapies for DM, since Wnt signaling as well as growth factors can affect vascular leakage in sensitive regions such as the retina as well as promote tumor development in the nervous system. WISP1, also a proliferative protein, can similarly lead to tumor growth while promoting reparative regeneration of tissues. Downstream, AMPK under some scenarios may result in the death of pancreatic islet cells. Yet, WISP1 also has been reported not only to be neuroprotective especially during DM, but also potentially block the spread of metastatic disease. Future development of novel strategies for metabolic disease in the nervous system must continue to elucidate the potential varied clinical outcomes of the Wnt and WISP1 pathways and precisely target mechanisms that drive outcomes for neuronal repair and regeneration.

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