



Prospects and Perspectives for WISP1 (CCN4) in Diabetes Mellitus

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Abstract: The prevalence of diabetes mellitus (DM) continues to increase throughout the world. In the United States (US) alone, approximately ten percent of the population is diagnosed with DM and another thirty-five percent of the population is considered to have prediabetes. Yet, current treatments for DM are limited and can fail to block the progression of multi-organ failure over time. Wnt1 inducible signaling pathway protein 1 (WISP1), also known as CCN4, is a matricellular protein that offers exceptional promise to address underlying disease progression and develop innovative therapies for DM. WISP1 holds an intricate relationship with other primary pathways of metabolism that include protein kinase B (Akt), mechanistic target of rapamycin (mTOR), AMP activated protein kinase (AMPK), silent mating type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*) (SIRT1), and mammalian forkhead transcription factors (FoxOs). WISP1 is an exciting prospect to foster vascular as well as neuronal cellular protection and regeneration, control cellular senescence, block oxidative stress injury, and maintain glucose homeostasis. However, under some scenarios WISP1 can promote tumorigenesis, lead to obesity progression with adipocyte hyperplasia, foster fibrotic hepatic disease, and lead to dysregulated inflammation with the progression of DM. Given these considerations, it is imperative to further elucidate the complex relationship WISP1 holds with other vital metabolic pathways to successfully develop WISP1 as a clinically effective target for DM and metabolic disorders.

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1. INTRODUCTION

1.1. The Growing Prevalence of Diabetes Mellitus

According to the Centers for Disease Control National Diabetes Statistics Report, almost thirty-five million individuals in the United States (US) which represents approximately ten percent of the population are diagnosed with diabetes mellitus (DM) [1]. At least seven million individuals over the age of 18 remain undiagnosed with DM and in the year 2018 it was estimated that almost thirty-five percent of adults in the US had prediabetes based on their fasting glucose and hemoglobin A1c (HbA1c) levels. Prevalence of DM also increased from nine and one-half percent during 1999 to 2002 to twelve percent during 2013 to 2016. In the adult population, it was noted that prevalence varied by indicators of socioeconomic status, such as education level. At least thirteen percent of adults with less than a high school education had DM compared to almost ten percent of individuals with a high school education and DM and seven and one-half percent of individuals with greater than a high

school education and DM. Risk factors for developing complications of DM included tobacco consumption, obesity, physical inactivity, hypertension, and elevated serum cholesterol [2]. In relation to financial burdens, the total direct and indirect estimated costs for the care of DM in the US was estimated at \$327 billion US Dollars in the year 2017 and excess medical costs per person were estimated at \$9,601 US dollars.

2. NOVEL STRATEGIES WITH WNT1 INDUCIBLE SIGNALING PATHWAY PROTEIN 1 (WISP1)

In light of the growing prevalence of DM and the significant number of individuals that remain undiagnosed with DM, new and innovative therapeutic strategies are critical to aid in the treatment of metabolic disorders, such as DM. Even under the best of circumstances, tight serum glucose control does not blunt the complications that can arise during DM [2, 3]. Careful nutritional and exercise management also is considered to be important for DM care, but in some cases these strategies may be less than beneficial dependent upon the degree of decreased oral intake and result in decreased organ mass through processes that involve autophagy (Table 1) [4].

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Table 1. Highlights.**Prospects and Perspectives for WISP1 (CCN4) in Diabetes Mellitus**

- The prevalence of diabetes mellitus (DM) continues to increase throughout the world with approximately ten percent of the population diagnosed with DM in the United States (US). The total direct and indirect estimated costs for the care of DM in the US is estimated at \$327 billion US Dollars on an annual basis.
- Current treatments for DM are limited and can fail to block the progression of multi-organ failure over time. Wnt1 inducible signaling pathway protein 1 (WISP1), also known as CCN4, offers an exciting prospect to address underlying disease progression and develop innovative therapies for DM.
- WISP1 has an intricate relationship with other primary pathways of metabolism that include protein kinase B (Akt), mechanistic target of rapamycin (mTOR), AMP activated protein kinase (AMPK), silent mating type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*) (SIRT1), and mammalian forkhead transcription factors (FoxOs).
- In conjunction with WISP1, Akt, mTOR, AMPK, SIRT1, and FoxOs can promote vascular as well as neuronal cellular protection and regeneration, control cellular senescence, block oxidative stress injury, and maintain glucose homeostasis.
- Yet, therapeutic targeting of WISP1 requires careful oversight to ensure a successful clinical outcome since WISP1 activity can promote tumorigenesis, lead to adipocyte hyperplasia and adipocyte hypertrophy, promote hepatic fibrosis, and result in vascular smooth muscle cell proliferation and migration that results in vascular restenosis.
- It is therefore critical for the development of new and innovative strategies for DM to focus not only on the fine modulation of WISP1, but also on the relationship WISP1 holds with vital metabolic pathways of Akt, mTOR, AMPK, SIRT1, and forkhead transcription factors to ensure efficacious and safe treatments for DM and metabolic disease.

Wnt1 inducible signaling pathway protein 1 (WISP1), a matricellular protein and a downstream target of the *wingless* pathway Wnt1 [5], offers exceptional promise to target DM and metabolic dysfunction that can address underlying disease progression [6, 7]. WISP, also known as CCN4, is a member of the CCN family of proteins. The CCN family of proteins contains six secreted extracellular matrix associated proteins. They are defined by the first three members of the family that include Cysteine-rich protein 61, Connective tissue growth factor, and Nephroblastoma over-expressed gene [8, 9]. WISP1 is present throughout the body that includes the brain, heart, kidney, lung, pancreas, placenta, epithelium, ovaries, small intestine, and spleen [9].

3. WISP1, METABOLIC DISORDERS, AND DIABETES MELLITUS

WISP1 has a number of important associations with metabolic disease and DM [6, 10]. WISP1 is one of several

genes that are over-expressed during pancreatic regeneration, suggesting that WISP1 may be necessary for the control of metabolic homeostasis [11]. WISP1 expression in visceral and subcutaneous fat tissue was found to be correlated with markers of insulin resistance and inflammation in glucose-tolerant subjects, suggesting a role for WISP1 during inflammation and obesity [12]. Circulating WISP1 also was found to be elevated during gestational DM and therefore may play a role in this disease process [13]. Increased levels of WISP1 are associated with glucose and lipid levels in obese children and adolescents that may be modulated by the pro-inflammatory cytokine interleukin 18 (IL-18) [14] that is independent of glycemic status [15] or insulin resistance [16]. Adipose deposits that can have a broad effect on DM are also associated with WISP1. In individuals with type 2 DM, WISP1 concentrations were positively correlated with the percentage of fat mass in the central abdominal area, as well as with serum levels of leptin, resistin and visfatin [17].

During DM, WISP1 may have a beneficial role to repair cells or tissue at risk. For example, WISP1 can be vital for stem cell differentiation [18]. WISP1 may have a protective role during traumatic brain injury through pathways involving autophagy [19-22]. WISP1 may promote vascular regeneration during saphenous vein crush injury that could be important during complications of DM [23]. WISP1 leads to vascular smooth muscle proliferation that can assist with tissue repair during toxic insults [24, 25]. WISP1 can oversee cellular senescence [26] that does not lead to excessive cellular proliferation in aging vascular cells [27] that is known to result in atherosclerosis during DM.

4. PROTECTION WITH WISP1, mTOR, SIRT1, AND FORKHEAD TRANSCRIPTION FACTORS

WISP1 can protect against cellular oxidative stress and β -amyloid (AB) with pathways of the mechanistic target of rapamycin (mTOR) [28] to inhibit proline rich Akt substrate 40 kDa (PRAS40) [29] and block TSC2 of the hamartin (tuberous sclerosis 1)/tuberin (tuberous sclerosis 2) (TSC1/TSC2) complex [30]. WISP1 also regulates the post-translational phosphorylation of AMP activated protein kinase (AMPK) for glucose homeostasis [31-34]. The ability of WISP1 to control AMPK activity is critical to modulate cellular metabolism during DM [35-38]. WISP1 oversees AMPK activation by differentially decreasing phosphorylation of TSC2 at serine¹³⁸⁷, a target of AMPK [39], and increasing phosphorylation of TSC2 at threonine¹⁴⁶² [30]. Through these pathways, WISP1 provides a minimal level of TSC2 and AMPK activity to control both cell survival and cell metabolism. WISP1 also has oversight of more upstream pathways of mTOR such as with protein kinase B (Akt). WISP1 prevents neuronal injury and mitochondrial dysfunction through Akt activation [40] and promotes silent mating type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*) (SIRT1) activity through autoregulatory control while depressing the mammalian forkhead transcription factor FoxO3a [41, 42]. WISP1, SIRT1, and FoxO3a also have been shown to function with melatonin in anti-aging pathways [27, 43, 44]. Under conditions of cardiac injury, WISP1 may be vital for tissue repair and pro-angiogenic behavior of coronary artery endothelial cells [45]. WISP1 through Akt has been shown to foster muscle stem cell growth and muscle regeneration [46]. WISP1 signaling plays a role in rescuing dopaminergic neurons during exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in rodent models of Parkinson's disease [47].

5. CHALLENGES AND CONSIDERATIONS FOR WISP1

Despite the multiple studies supporting a protective role for WISP1, WISP1 targeting for clinical disease requires careful oversight [48]. Through pro-angiogenic pathways, WISP1 can foster tumorigenesis, such as osteosarcoma [49], breast cancer [50], and gastric cancer [8]. WISP1 also has been associated with obesity progression since WISP1 can promote mesenchymal stem cells and lead to adipocyte hyperplasia and hypertrophy [51]. WISP1 may promote dysregulated inflammation during injury, such as in times of sepsis [52] and in tumor microenvironments [53]. Through

Akt, WISP1 can foster the proliferation of human vascular smooth muscle cells that ultimately may lead to vascular restenosis [54]. During chronic alcohol consumption, WISP1 may be responsible for hepatocyte proliferation and the development of liver cancer [55] and under other conditions WISP1 may result in the development of hepatic fibrosis [56]. These changes in hepatic function may alter gluconeogenesis and impair glucose homeostasis [57]. During metabolic disease, WISP1 in conjunction with other pathways may foster the development of gestational DM [13]. WISP1 also may affect the progression of uremia and modulate the epithelial-mesenchymal transition process in renal tubular epithelial cells, a process that can impact hepatic metabolism of drugs [58].

CONCLUSION AND FUTURE PERSPECTIVES

WISP1 opens up a number of new considerations for developing innovative treatments for metabolic disorders such as DM. In the US alone, almost 35 million individuals, approximately ten percent of the population, suffer with DM and another seven million individuals over the age of 18 remain undiagnosed with DM. The financial implications for the treatment of DM are problematic with the total direct and indirect estimated costs for the annual care of DM in the US to equal \$327 billion US Dollars. Present therapies for DM that include pharmacological interventions for glucose control, nutritional management, and physical activity are less than completely effective and warrant new avenues of consideration to aid in treatment.

Recent work highlights the intimate association of WISP1 with DM. WISP1 may be required for pancreatic regeneration and metabolic homeostasis, may assist with vascular regeneration during injury, may oversee pathways of inflammation and obesity, control cellular senescence, and has been correlated with fat mass and adipose deposits as well as with leptin, resistin and visfatin levels during type 2 DM. Through pathways that involve Akt, mTOR, AMPK, and autophagy, WISP1 can provide cellular protection against oxidative stress. Furthermore, WISP1 in conjunction with SIRT1 and FoxO3a may promote anti-aging pathways and be critical for tissue repair and pro-angiogenic behavior of endothelial cells during injury to the nervous and cardiac systems.

However, therapeutic targeting of WISP1 requires careful oversight to ensure a successful clinical outcome. WISP1 activity can promote tumorigenesis through pro-angiogenic pathways, lead to mesenchymal stem cell proliferation, adipocyte hyperplasia, and adipocyte hypertrophy, and result in vascular smooth muscle cell proliferation and migration that results in vascular restenosis. Hepatic disease also may ensue with WISP1 that leads to cancer and liver fibrosis. As a result of these challenges with WISP1, it becomes imperative for the successful development of new and innovative strategies for DM to focus not only on the fine modulation of WISP1, but also on the close relationship WISP1 holds with vital metabolic pathways of Akt, mTOR, AMPK, SIRT1, and forkhead transcription factors to ensure successful future treatments for DM.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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