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Cognitive impairment with diabetes mellitus and metabolic disease: innovative insights with the mechanistic target of rapamycin and circadian clock gene pathways

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Abstract

Introduction: Dementia is the 7th leading cause of death that imposes a significant financial and service burden on the global population. Presently, only symptomatic care exists for cognitive loss, such as Alzheimer's disease.

Areas Covered: Given the advancing age of the global population, it becomes imperative to develop innovative therapeutic strategies for cognitive loss. New studies provide insight to the association of cognitive loss with metabolic disorders, such as diabetes mellitus.

Expert Opinion: Diabetes mellitus is increasing in incidence throughout the world and affects 350 million individuals. Treatment strategies identifying novel pathways that oversee metabolic and neurodegenerative disorders offer exciting prospects to treat dementia. The mechanistic target of rapamycin (mTOR) and circadian clock gene pathways that include AMP activated protein kinase (AMPK), Wnt1 inducible signaling pathway protein 1 (WISP1), erythropoietin (EPO), and silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1) provide novel strategies to treat cognitive loss that has its basis in metabolic cellular dysfunction. However, these pathways are complex and require precise regulation to maximize treatment efficacy and minimize any potential clinical disability. Further investigations hold great promise to treat both the onset and progression of cognitive loss that is associated with metabolic disease.

Keywords

Alzheimer's disease; AMPK; circadian clock genes; diabetes mellitus; dementia; erythropoietin; mTOR; SIRT1; WISP1

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Declaration of Interest

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1.0 Introduction and Background

1.1. Neurodegenerative Disorders and the Impact of Dementia

As a result of improvements in global healthcare and the progressive increase in life span, neurodegenerative disorders will continue to increase in prevalence among the world's population. If one focuses on cognitive disorders, it is interesting to note that dementia is now considered to be the 7th leading cause of death. According to the World Health Organization [1], the present numbers for the prevalence and treatment costs for dementia are significant and affect all countries. For example, the incidence of sporadic cases of Alzheimer's disease (AD) is expected to significantly increase throughout the globe [2,3]. Cognitive disorders such as AD affect more than 5 million individuals in the United States (US) alone [4,5]. At least sixty percent of dementia cases are believed to result from AD [5-8]. At minimum, five percent of the world's elderly population suffer from dementia. This is equal to almost 50 million individuals and new cases each year are increasing at an alarming rate. By the year 2030, 82 million people are expected to have dementia. Projected out another twenty years to 2050, 152 million will suffer from dementia.

The financial and service burdens for dementia are equally staggering. More than $800 billion United States dollars (USD) are spent to care for individuals with dementia on an annual basis. These costs are close to two percent of the global gross domestic product. By the year 2030, medical and social services could reach in the US to two trillion USD annually with the ability to easily overwhelm the system. These projections do not include the significant financial costs that involve social and adult living care as well as informal and companion care for individual families. In addition, the World Health Organization estimates the need for close to sixty million new health and social care workers. When to address the need for these healthcare workers in a timely and efficient manner can be a difficult consideration since the onset and progression of dementia in individuals is not always well recognized. Furthermore, dementia and cognitive loss are considered to be under diagnosed throughout the world. Once diagnosis is correctly performed, it can be in the late or end stages of the disease, leaving little utility for treatment and possibly offering fragmented care.

1.2 Metabolic Disease, Diabetes Mellitus, and Dementia

Recent studies highlight the previously unrecognized link between metabolic disorders and cognitive loss. Disorders such as diabetes mellitus (DM) hold an increased risk for the onset and progression of AD and cognitive loss [3,9-12]. Similar to neurodegenerative disorders and dementia, DM is increasing in incidence throughout the world. Approximately 350 million individuals currently have DM [13-17]. An additional 8 million individuals are believed to suffer from metabolic disorders but remain undiagnosed at present [18-20]. The care for patients with DM also extracts a significant portion of healthcare resources. In the US, DM care accounts for seventeen percent of the Gross Domestic Product per the Centers for Medicare and Medicaid Services (CMS) [21]. Almost $176 billion is required for direct medical costs and another $69 billion in lost finances results from reduced productivity tied to DM.

Equally as important to recognize is that DM affects multiple systems of the body [3,10,12,22-25]. DM has been tied to mental illness [26,27], vascular brain injury [7,28-32], cardiovascular disease, immune function , and stem cell regulation [7,32-36]. In relation to cognitive loss and AD, diabetes can affect multiple pathways in these disorders and lead to disease progression [7,32-36].

2.0. Exploring Novel Targets for Dementia and Cognitive Loss

Neurodegenerative disorders, and in particular, cognitive loss can have multiple origins that lead to disease onset and progression. Risk factors for cognitive loss include tobacco use, low education in early life, and hypertension. Yet, new insights point to DM as a significant risk factor that affects large numbers of the global population. Early diagnosis of DM with rapid induction of available therapies for DM can offer some degree of improvement and slow the progression of DM. However, tight serum glucose control does not always lead to the resolution of complications from DM [14,37]. Use of diet and body mass control treatments may be effective to prevent hyperglycemic events, but these strategies also can potentially decrease organ mass through processes that involve autophagy [38]. Furthermore, most available treatments that are directed to treat AD alone involve the use of cholinesterase inhibitors [39]. Dementia that may be caused by vascular disease may be treated with therapies that focus on vascular and metabolic disorders, such as DM [40]. Yet, these treatments for the most part are symptomatic. As a result of these severe limitations to target cognitive loss during metabolic dysfunction, addressing novel pathways for future clinical work that can oversee both metabolic disease and neurodegenerative disorders may offer extremely valuable and exciting avenues to overcome cognitive loss. These innovative strategies involve the mechanistic target of rapamycin (mTOR) and circadian clock gene pathways that include AMP activated protein kinase (AMPK), Wnt1 inducible signaling pathway protein 1 (WISP1), erythropoietin (EPO), and silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1).

3.0. Cellular Pathways of the Mechanistic Target of Rapamycin

One possible target for innovative strategies to treat cognitive loss through metabolic pathways is the mechanistic target of rapamycin (mTOR), a 289-kDa serine/threonine protein kinase that is encoded by a single gene *FRAP1* [10,41-43] (Figure 1). mTOR also is known as the mammalian target of rapamycin and the FK506-binding protein 12-rapamycin complex-associated protein 1 [8]. The target of rapamycin (TOR) was initially described in *Saccharomyces cerevisiae* with the genes *TOR1* and *TOR2* [8]. Using rapamycin-resistant TOR mutants, *TOR1* and *TOR2* were found to encode the Tor1 and Tor2 isoforms in yeast [44]. Rapamycin is a macrolide antibiotic in *Streptomyces hygroscopicus* that blocks TOR and mTOR activity [45]. Subsequently it was found that mTOR forms the principal component of the protein complexes mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2) [46-48]. Rapamycin can prevent mTORC1 activity by binding to immunophilin FK-506-binding protein 12 (FKBP12) that attaches to the FKBP12 -rapamycin-binding domain (FRB) at the carboxy (C) -terminal of mTOR to interfere with the FRB domain of mTORC1. mTORC1 appears to be more sensitive to inhibition by rapamycin than mTORC2,

but chronic administration of rapamycin can inhibit mTORC2 activity as a result of the disruption of the assembly of mTORC2 [49,50].

3.1 mTORC1

mTORC1 and mTORC2 are divided into subcomponents (Figure 1). mTORC1 is composed of Raptor, the proline rich Akt substrate 40 kDa (PRAS40), Deptor (DEP domain-containing mTOR interacting protein), and mammalian lethal with Sec13 protein 8, termed mLST8 (mLST8/G□L) [8]. mTORC1 can bind to its constituents through the protein Ras homologue enriched in brain (Rheb) that phosphorylates the Raptor residue serine^{863} and other residues that include serine^{859}, serine^{855}, serine^{877}, serine^{696}, and threonine^{706} [51]. The inability to phosphorylate serine^{863} limits mTORC1 activity, as shown using a site-direct mutation of serine^{863} [52]. mTOR can control Raptor activity and this activity can be blocked by rapamycin [52]. Deptor, an inhibitor as well, blocks mTORC1 activity by binding to the FAT (FKBP12 -rapamycin-associated protein (FRAP), ataxia-telangiectasia (ATM), and the transactivation/transformation domain-associated protein) domain of mTOR. If the activity of Deptor is diminished, protein kinase B (Akt), mTORC1, and mTORC2 activities are increased [53]. PRAS40 also blocks mTORC1 activity by preventing the association of p70 ribosomal S6 kinase (p70S6K) and the eukaryotic initiation factor 4E (eIF4E)-binding protein 1 (4EBP1) with Raptor [54,55]. mTORC1 becomes active once PRAS40 is phosphorylated by Akt. This releases PRAS40 from Raptor to sequester PRAS40 in the cell cytoplasm with the docking protein 14-3-3 [56-60]. mLST8, in contrast to Deptor and PRAS40, promotes mTOR kinase activity. This involves the binding of p70S6K and 4EBP1 to Raptor [61]. Interestingly, mLST8 also controls insulin signaling through the transcription factor FoxO3 [62,63], is necessary for Akt and protein kinase C-α (PKCα) phosphorylation, and is required for Rictor to associate with mTOR [62].

3.2 mTORC2

mTORC2 has both similarities and differences to mTORC1. mTORC2 is composed of Rictor, mLST8, Deptor, the mammalian stress-activated protein kinase interacting protein (mSIN1), and the protein observed with Rictor-1 (Protor-1) [54]. mTORC2 controls cytoskeleton remodeling through PKCα and cell migration through the Rac guanine nucleotide exchange factors P-Rex1 and P-Rex2 and through Rho signaling [64]. mTORC2 activates protein kinases that includes glucocorticoid induced protein kinase 1 (SGK1), a member of the protein kinase A/protein kinase G/protein kinase C (AGC) family of protein kinases. Protor-1, a Rictor-binding subunit of mTORC2, activates SGK1 [65,66]. The kinase domain of mTOR phosphorylates mSIN1 and prevents lysosomal degradation of this protein. Rictor and mSIN1 also can phosphorylate Akt at serine^{473} and foster threonine^{308} phosphorylation by phosphoinositide-dependent kinase 1 (PDK1) to enhance cell survival.

3.3 AMP activated protein kinase (AMPK)

In regards to metabolic disease, the AMP activated protein kinase (AMPK) is closely tied to the mTOR pathway through the hamartin (tuberous sclerosis 1)/tuberin (tuberous sclerosis 2) (TSC1/TSC2) complex that inhibits mTORC1 [5,67] (Figure 1). Control of the TSC1/TSC2 complex also is overseen through Akt and its phosphorylation of TSC2. Extracellular signal-regulated kinases (ERKs), protein p90 ribosomal S6 kinase 1 (RSK1), and glycogen

synthase kinase −3β (GSK-3β) also can modulate the activity TSC1/TSC2 complex. AMPK can inhibit mTORC1 activity through the activation of the TSC1/TSC2 complex [68,69]. TSC2 functions as a GTPase-activating protein (GAP) that converts G protein Rheb (Rheb-GTP) into the inactive GDP-bound form (Rheb-GDP). Once Rheb-GTP is active, Rheb-GTP associates with Raptor to oversee the binding of 4EBP1 to mTORC1 and increase mTORC1 activity [70]. AMPK phosphorylates TSC2 to increase GAP activity to change Rheb-GTP into the inactive Rheb-GDP and to block mTORC1 activity [71].

AMPK has been shown to reduce insulin resistance, since the loss of AMPK results in reduced tolerance to the development of insulin resistance [72]. AMPK also is involved in the protection of endothelial progenitor cells during periods of hypeglycemia [73]. During periods of dietary restriction that may increase lifespan, AMPK can be one factor to shift to oxidative metabolism [74]. AMPK can reduce ischemic brain damage in diabetic animal models [75]. In addition, during periods of hyperglycemia, AMPK activity may be necessary to increase basal autophagy activity [76,77] and maintain endothelial cell survival [78,79].

AMPK activation can improve memory retention in models of AD and DM [80], limit cardiac ischemia in animal models, and prevent adipocyte differentiation, lipid accumulation, and obesity [45]. Metformin, an agent that controls hyperglycemia in DM, also inhibits mTOR activity and leads to the induction of autophagy. Metformin can activate AMPK [81] and block mTOR activity through additional pathways independent of AMPK [82]. Metformin prevents cell loss during hypoxia through increased AMPK activity [83], provides neuroprotection [29], limits cardiomyopathy in experimental models of DM [84] and prevents endothelial cell senescence [85]. Yet, the necessary level of AMPK activity to offer cellular protection during metabolic activity is not completely understood. In some cases, limited AMPK activity may be better for cellular protection in DM. Reduced AMPK activity can promote the protection of pancreatic islet cells in mice [86], limit amyloid (Aβ) toxicity [87], and prevent inflammation in the nervous system [88].

3.4 mTOR, *Wingless* pathway, and Wnt1 inducible signaling pathway protein 1 (WISP1)

The *wingless* pathway of Wnt proteins represents cysteine-rich glycosylated proteins that control processes involving metabolism, neuronal development, angiogenesis, immunity, tumorigenesis, fibrosis, and stem cell proliferation [89-92]. In the nervous system, Wnt signaling may be instrumental in the pathogenesis of neurodegenerative disorders [6,93-95]. Wnt signaling and its family member Wnt1 can block autophagy [96-99] and apoptotic endothelial cell injury during elevated glucose exposure [100]. Wnt signaling also promotes human β-cell proliferation [101], fosters the repair of diabetic wounds [102], impacts the vasculature of the brain [103], and prevents cognitive decline during aging and during DM [104]. Components of the Wnt pathway also have increased expression in the brain during periods of exercise [105] that may assist against insulin resistance.

A downstream target in the Wnt1 pathway is the Wnt1 inducible signaling pathway protein 1 (WISP1) (Figure 1). The CCN family member WISP1 has a significant role in cellular metabolism [24,90-92] that is dependent upon mTOR signaling pathways [106,107]. The CCN family of proteins has 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 [108,109]. WISP1 is a matricellular protein and a downstream target of the *wingless* pathway Wnt1 that can oversee metabolism [89]. WISP1 expression is affected by weight change in humans and increases during insulin resistance in children and adolescents [92]. WISP1 production also is increased during gestational diabetes [91]. As a result, WISP1 may represent an important reparative process in individuals with DM [63]. WISP1 can modulate cellular senescence [110] to a degree that does not promote excessive cellular proliferation in aging vascular cells [111] that could lead to atherosclerosis during DM. WISP1 also is one of several genes that are over-expressed during pancreatic regeneration, indicating that WISP1 may assist with protection of tissues necessary for metabolic homeostasis [112].

WISP1 leads to mTOR activation to block PRAS40 [58] and TSC2 [87] to protect cells against oxidative stress. WISP1 controls the post-translational phosphorylation of AMPK for glucose homeostasis [8,48,113,114]. It is the ability of WISP1 to control AMPK activity that becomes vital to control cellular metabolism during DM [48]. WISP1 modulates AMPK activation by differentially decreasing phosphorylation of TSC2 at serine^{1387}, a target of AMPK, and increasing phosphorylation of TSC2 at threonine^{1462}, a target of Akt [87]. This enables WISP1 to provide a minimal level of TSC2 and AMPK activity to control in dual fashion both cell survival and cell metabolism. AMPK activity levels can become an important factor for cellular survival. Increased AMPK activity can reduce insulin resistance and oxidative stress mediated through the activation of autophagy [72]. AMPK activation can correct metabolic parameters of cells and prevent adipocyte differentiation, lipid accumulation, and obesity [115]. However, under some conditions, increased AMPK activity can be detrimental. As previously noted, reduced AMPK activity is necessary to promote the protection of pancreatic islet cells in mice [86], limit amyloid (Aβ) toxicity [87], and prevent nervous system inflammation [88].

3.5 mTOR, Metabolism, and Erythropoietin

mTOR activation can control cellular metabolism and insulin signaling. mTOR pathways that include p70S6K and 4EBP1 can improve insulin secretion in pancreatic β-cells and increase resistance to β-cell streptozotocin toxicity and obesity in mice [116]. Loss of p70S6K activity results in hypo-insulinemia, insulin insensitivity to glucose secretion, glucose intolerance, and decreased pancreatic β-cell size [117]. Rapamycin administration leads to reduced β-cell function and mass, insulin resistance, decreased insulin secretion, and the induction of DM [118]. Although inhibition of mTOR activity with rapamycin can limit food intake and prevent fat-diet induced obesity in mice [119] and sometimes offer protection [120], rapamycin can impair glucose uptake and increase mortality in models of Type 2 DM [121]. Rapamycin and inhibition of mTOR blocks insulin generated Akt activation and alters the translocation of glucose transporters to the plasma membrane in skeletal muscle [119]. Activation of mTOR can protect pancreatic β- cells against cholesterol-induced apoptosis [122] and glucolipotoxicity [123]. Recently, the protective role of mTOR in areas such as the Mediterranean diet has been tied to a reduction in Aβ toxicity in astrocytes through enhanced Akt activity by consumption of polyphenol of olives and olive oil that ultimately could prevent the onset or progression of AD [124].

Yet, there appears to be feedback systems “built-in” with mTOR and cellular metabolic regulation. mTOR can function in a negative feedback loop and potentially produce glucose intolerance by inhibiting the insulin receptor substrate 1 (IRS-1). In studies with high fat fed obese rats, mTOR leads to inhibitory phosphorylation of IRS-1, impaired Akt signaling, and insulin resistance [125]. Activation of mTOR signaling with p70S6K can phosphorylate IRS-1 in the renin-angiotensin-aldosterone system during consumption of high fat diets that results in high circulating angiotensin II (ANG II) and insulin resistance [126].

mTOR also can rely upon growth factors that have defined clinical utility, such as erythropoietin (EPO) (Figure 1), to provide cellular protection during DM. The *EPO* gene is located on chromosome 7 and is a single copy in a 5.4 kb region of the genomic DNA [127]. This gene encodes for a polypeptide chain protein that has initially 193 amino acids [128]. EPO is then processed with the removal of a carboxy-terminal arginine^{166} in the mature human and recombinant human EPO (rhEPO). A protein of 165 amino acids with a molecular weight of 30.4 kDa is subsequently generated [129-132]. EPO, an erythropoiesis-stimulating agent, is approved for the treatment of anemia during chronic kidney failure, human immunodeficiency virus, and chemotherapy. EPO is present in the brain, uterus, and liver [133-137], but the primary site for the production and secretion of EPO is the kidney peritubular interstitial cells. EPO expression is controlled by changes in oxygen tension and not by the concentration of red blood cells [19,133,138].

EPO has a number of neuroprotective functions [139-141], uses multiple novel pathways to affect biological systems [6,128,142,143], may limit cognitive decline and AD [144], and affects metabolic pathways [145,146]. EPO controls pathways of apoptosis and autophagy through mTOR that can affect neuronal regeneration [147]. EPO prevents apoptotic cell death during Aβ exposure through mTOR to prevent caspase activation [58]. In addition, EPO can promote microglial survival during oxidative stress through mTOR signaling [148]. EPO oversees mTOR, Akt [142,149,150], and down-stream signaling pathways that involve proline rich Akt substrate 40 kDa (PRAS40) to enhance neuronal survival during oxygen-glucose deprivation [56]. EPO also relies upon mTOR during hypoxia-reoxygenation stress to protect hippocampus-derived neuronal cells [151].

In relation to cellular metabolism [15,47], EPO can reduce blood glucose levels in animal models of DM and obesity [152], promote wound healing during DM [153], and protect endothelial cells during experimental models of DM [100,154]. EPO can block the detrimental effects of obesity in animal models [132], preserve cellular mitochondrial function [148,155-158] and energy metabolism [131], and limit oxidative stress and apoptosis in Schwann cells mediated by advanced glycation end products (AGEs) [159].

EPO also governs the AMPK pathway and autophagy [160]. In some cases, EPO can protect against neuronal injury through increased AMPK activity and enhanced autophagy activity [161]. EPO can control AMPK and mTOR activities to protect cells under conditions of oxidative stress [87]. EPO also relies upon AMPK pathways for anti-oxidant gene expression [162] and oversees inflammation in the nervous system through AMPK [47]. EPO blocks apoptotic cell injury through AMPK by increasing autophagy-related signaling pathways [161]. The oversight of inflammation in the nervous system by EPO is intimately

connected to AMPK [163]. It is the concentration and activity of EPO that can influence the protective actions of mTOR and signaling pathways associated with AMPK. EPO modulates a specific level of AMPK and mTOR activity to alleviate detrimental effects of oxidative stress [56,162]. This fine control over mTOR is important since high concentrations of EPO can lead to cellular damage and actually diminish the activity of mTOR [164].

PI 3-K and Akt that enhance mTOR activity also are critical pathways that provide cellular protection through EPO. EPO can phosphorylate Akt at serine^{473} to activate Akt [128,142,165,166]. EPO signaling through Akt activation has been shown to protect against hypoxia-reoxygenation stress [151] and EPO may control intracellular calcium levels to preserve mitochondrial function [45,131,155,167,168]. EPO also can increase cell survival through Akt activation during Aβ toxicity [169-171] and oxidative stress [56,148,172-174].

4.0. Clock Genes and Cellular Metabolism

Circadian rhythm clock genes play a significant role with neurodegenerative disease and cognitive loss [175,176] (Figure 1), as well as other disorders such as cancer [2,177-179]. The master mammalian circadian clock is in the suprachiasmatic nucleus (SCN) located above the optic chiasm and receives light input from photosensitive ganglion cells in the retina. The SCN controls most overt circadian rhythms and depends upon the pineal gland, hypothalamic nuclei, and vasoactive intestinal peptide to oversee processes that involve the sleep wake cycle, release of hormones cortisol and melatonin, oxidative stress responses [180], and the regulation of body temperature [181]. In the clock gene family, members of the basic helix-loop-helix -PAS (Period-Arnt-Single-minded) transcription factor family, such as CLOCK and BMAL1 [182], control the expression of the genes *Cryptochrome (Cry1 and Cry2)* and *Period (Per1, Per2, and Per3).* Feedback is provided by PER:CRY heterodimers that translocate to the nucleus to block the transcription activated by CLOCK:BMAL1 complexes. Additional regulatory loops consist of retinoic acid-related orphan nuclear receptors REV-ERBα, also known as NR1D1 (nuclear receptor subfamily 1, group D, member 1), and RORα that are activated by CLOCK:BMAL1 heterodimers. The REV-ERBα and RORα receptors bind retinoic acid-related orphan receptor response elements (ROREs) present in the BMAL1 promoter to repress and activate rhythmic transcription of BMAL1 by RORs and REV-ERBs, respectively. REV-ERBs can repress transcription to result in circadian oscillation of BMAL1 [183,184].

The clock gene pathway is affected during dementia disorders. Rhythmic methylation of BMAL1 is changed in the brains of patients with AD, suggesting that alterations in the DNA methylation of clock genes may contribute to cognitive loss and behavior changes [185]. Animal models of Parkinson's disease with 6-hydroxydopamine (6-OHDA), a disorder also associated with cognitive loss, show that decreased BMAL1 and RORα persisted with levodopa treatment, indicating that chronic or long-term levodopa treatment may impair circadian rhythm function [186]. Clock genes also impact lifespan during neurodegenerative disorders. In studies with *Drosophila melanogaster*, lifespan was reduced in three arrhythmic mutants involving ClkAR, cyc0 and tim0. ClkAR mutants had significant faster age-related locomotor deficits that were similar to Parkinson's disease. Restoring Clk function rescued *Drosophila* from the locomotor deficits. An increase in oxidative stress was noted with the

mutant phenotypes, but deficits appeared to correlate best with loss of dopaminergic neurons, similar to Parkinson's disease, rather than directly to the presence of oxidative stress in this case [187].

Circadian rhythm dysfunction during cognitive loss and aging has been associated with autophagy induction [188]. In animal models of AD, a basal circadian rhythm that governs macroautophagy may be necessary to limit cognitive decline and Aβ deposition [189]. Interestingly, changes in the external environment can affect circadian rhythm that affects cognition function [176]. For example, chronic sleep fragmentation has been shown to affect autophagy proteins in the hippocampus [190] that can impair memory and cognition [5,191-194]. Autophagy in the hippocampus also is blocked during the absence of the PER1 circadian clock protein that may worsen the pathology of cerebral ischemia [195], suggesting that PER1 circadian clock protein is necessary for neuroprotection.

4.1 Circadian Rhythm and mTOR

The control of circadian pathways are closely tied to mTOR [196-198] (Figure 1). Melatonin, a pineal hormone that is involved in regulating circadian rhythm, depends upon autophagy pathways and mTOR to control processes of aging and neurodegeneration [199]. Loss of mTOR activation has been shown to alter circadian rhythm and cognitive decline during prolonged space flight and microgravity [200]. Furthermore, cerebral ischemic infarction may be influenced by an alteration in circadian rhythm genes and fluctuations in mTOR activity [195,201].

4.2 Circadian Rhythm and SIRT1

The role of mTOR may extend beyond its internal pathways to oversee circadian rhythm and involve the silent mating type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*) (SIRT1) [7,202-204] (Figure 1). SIRT1 may be a significant component to regulate the activity of mTOR during metabolic regulation and cognition. Genes with the greatest statistical change following caloric restriction in mice have included those associated with sirtuin activation and mTOR inhibition [205]. SIRT1 can increase lifespan in higher organisms [77,206-209], can be associated with neuroprotection and cognition [206,210], and provides protection against oxidative stress [24,211-214]. SIRT1 inhibits mTOR pathways through AMPK. SIRT1 has an inverse relationship with mTOR in embryonic stem cells [15,47] and can block mTOR to promote autophagy. In relation to circadian rhythm, SIRT1 has been associated with circadian rhythm dysfunction that affects the development of cognitive disorders such as AD [175]. SIRT1 control of circadian rhythm and melatonin also may affect glucose tolerance and DM [181] as well as inflammation during obesity [215]. Increased SIRT1 activity with a disruption in circadian rhythm results in additional disorders such as increased susceptibility to mammary carcinogenesis [216]. Yet, SIRT1 may be beneficial under specific circumstances to regulate circadian rhythm gene expression that can foster hepatocellular proliferation and liver regeneration following liver resection [217]. More recent work also suggests an important role for SIRT1 targets with aging and circadian gene expression in the liver [218].

These studies suggest that specifically controlled activities of mTOR and SIRT1 are required to achieve optimal control over metabolic and cognitive function. A decrease in SIRT1 activity that would mirror an increase in mTOR activity is associated with neural differentiation and the maturation of embryonic cortical neurons [219]. Differentiation of human embryonic stem cells into motoneurons also occurs with decreased SIRT1 activity. In contrast, increased activity of SIRT1 through microRNA-34a can promote the apoptotic cell death of mesenchymal stem cells [220].

5.0. Expert Opinion

With the significant increase in neurodegenerative disorders throughout the globe and especially those disease entities that affect cognition, it is imperative that innovative strategies are developed to provide treatment for individuals that suffer from cognitive loss and dementia (Article Highlights). Dementia is now considered to be the 7th leading cause of death with staggering financial and service burdens. At present, only limited symptomatic treatments exist for these individuals. New studies are now highlighting the previously unrecognized association between metabolic disorders and dementia, including AD. DM alone is increasing in incidence throughout the world and almost 350 million individuals currently have DM. Early diagnosis of DM with use of available therapies for DM can offer some degree of improvement. However, tight serum glucose control does not always prevent complications from DM [14,37]. Reduced diet and body mass control treatments may be effective to prevent hyperglycemic events, but these treatments may decrease organ mass through processes that involve autophagy [38]. To a similar extent, most available treatments that are directed to treat AD alone involve the use of cholinesterase inhibitors [39] which have limited efficacy. Given these severe limitations for dementia during metabolic dysfunction, addressing novel pathways that can oversee metabolic disease and cognitive loss may offer critical therapies to overcome dementia. The pathways of mTOR, AMPK, WISP1, EPO, circadian clock genes, and SIRT1 offer exciting prospects to treat cognitive loss that has its basis in metabolic cellular dysfunction. Interestingly, identification of mTOR activity in the Mediterranean diet has been tied to a reduction in Aβ toxicity in astrocytes through enhanced Akt activity by consumption of polyphenol of olives and olive oil. This work suggests that such a diet through mTOR control of cellular metabolism could potentially prevent the onset or progression of AD [124]. However, this course has a number of challenges. These pathways ultimately require fine biological control to prevent cellular demise and unwanted clinical disability. For example, mTOR can function in a negative feedback loop and potentially produce glucose intolerance by inhibiting the insulin receptor substrate 1 (IRS-1) [125]. In addition, AMPK activation can improve memory retention in models of AD and DM [80], prevent lipid accumulation and obesity [45], and promote neuroprotection [29]. Yet, in some scenarios, reduced AMPK activity is required to promote the protection of pancreatic islet cells in mice [86], limit Aβ toxicity [87], and prevent inflammation in the nervous system [88]. Additional work suggests that specifically controlled activities of mTOR and SIRT1 are required to control metabolic and cognitive function. At times, increased activity of SIRT1 through microRNA-34a can be detrimental, such as promoting the apoptotic cell death of mesenchymal stem cells [220]. Furthermore, these pathways can be proliferative in nature, such as WISP1, and lead to tumorigenesis

[109]. As a result, continued work is required to further unravel the complex functions of these pathways for the promotion of drug development success and limit negative clinical outcomes during cognitive loss and metabolic dysfunction.

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Article Highlights

- Improvements in global healthcare and the progressive increase in life span have led to increased prevalence of neurodegenerative disorders and dementia, such as Alzheimer's disease, in the world's population
- Recent studies highlight the previously unrecognized link between metabolic disorders, such as diabetes mellitus, and cognitive loss
- The mechanistic target of rapamycin (mTOR), a principal component for mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2), and circadian clock genes are exciting novel targets to treat cognitive loss through metabolic pathways
- mTOR and circadian clock genes are intimately linked to AMP activated protein kinase (AMPK), Wnt1 inducible signaling pathway protein 1 (WISP1), erythropoietin (EPO), and silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1) to oversee cellular metabolic homeostasis and cognitive function
- mTOR and circadian clock genes in association with their downstream pathways offer fruitful prospects to preserve neuronal and vascular function through apoptotic and autophagic pathways, but are complex in nature requiring fine biological control to further the development of effective treatment strategies and limit the potential for negative clinical outcomes

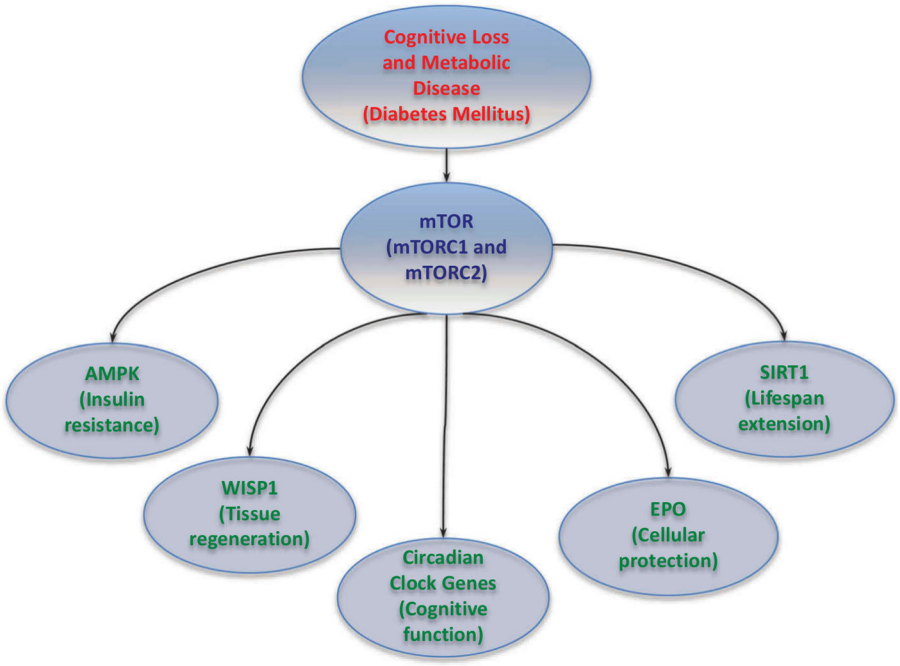

Figure 1: Innovative Strategies for Cognitive Loss.

With the advancing age of the global population and the increased prevalence of dementia, it is critical to develop innovative therapeutic strategies for cognitive loss. New work and the identification of novel pathways provide insight into the increased risk for the onset of cognitive loss associated with metabolic disorders. mTOR forms the complexes mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2) and is integrated with a number of pathways that include AMP activated protein kinase (AMPK) (affects insulin resistance), Wnt1 inducible signaling pathway protein 1 (WISP1) (associated with tissue regeneration), circadian clock genes (oversee cognitive function), erythropoietin (EPO) (controls cellular protection), and silent mating type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*) (SIRT1) (governs lifespan extension). These pathways with careful biological control hold great promise for the successful and safe treatment of cognitive loss that is associated with metabolic dysfunction such as diabetes mellitus.