Neurodegeneration, memory loss, and dementia: the impact of biological clocks and circadian rhythm

Kenneth Maiese

Cellular and Molecular Signaling, New York, NY 10022, USA

Abstract

Introduction: Dementia and cognitive loss impact a significant proportion of the global population and present almost insurmountable challenges for treatment since they stem from multifactorial etiologies. Innovative avenues for treatment are highly warranted.

Methods and results: Novel work with biological clock genes that oversee circadian rhythm may meet this critical need by focusing upon the pathways of the mechanistic target of rapamycin (mTOR), the silent mating type information regulation 2 homolog 1 (Saccharomyces cerevisiae) (SIRT1), mammalian forkhead transcription factors (FoxOs), the growth factor erythropoietin (EPO), and the wingless Wnt pathway. These pathways are complex in nature, intimately associated with autophagy that can maintain circadian rhythm, and have an intricate relationship that can lead to beneficial outcomes that may offer neuroprotection, metabolic homeostasis, and prevention of cognitive loss. However, biological clocks and alterations in circadian rhythm also have the potential to lead to devastating effects involving tumorigenesis in conjunction with pathways involving Wnt that oversee angiogenesis and stem cell proliferation.

Conclusions: Current work with biological clocks and circadian rhythm pathways provide exciting possibilities for the treating dementia and cognitive loss, but also provide powerful arguments to further comprehend the intimate and complex relationship among these pathways to fully potentiate desired clinical outcomes.

Keywords
Alzheimer’s disease; Autophagy; Circadian rhythm; Dementia; Erythropoietin; Forkhead; FoxO; Mechanistic target of rapamycin (mTOR); Parkinson’s disease; Silent mating type information regulation 2 homolog 1; wingless ; Wnt
2. Introduction

Neurodegenerative disorders pose a significant challenge for diagnosis, preventing disease progression, and providing treatment. Cognitive loss in relation to Alzheimer’s disease (AD) is an excellent example since diseases that include AD are the result of multiple underlying mechanisms [1–6] (Table 1). For example, many pathways may lead to memory loss and involve neuronal and vascular cell injury related to metabotropic receptors, lipid dysfunction, cellular metabolic dysfunction with diabetes mellitus (DM), astrocytic cell injury, β-amyloid (Aβ), heavy metal disease, loss of access to bright light, tau, mitochondrial damage, oxidative stress, acetylcholine loss, and excitotoxicity [1, 3, 6–30].

In addition, cognitive disorders raise significant financial concerns [1, 31–34]. Greater than 800 billion United States dollars (USD) per year are required to treat dementia equaling approximately 2 percent of the global Gross Domestic Product. Social and medical services by the year 2030 may possibly equal 2 trillion USD per year in the United States. Currently, greater than 5 million patients have AD and it is estimated that 4 million receive care at a yearly cost of 3.8 billion USD. Furthermore, the market revenue to provide treatments for AD may not be fully appreciated, but at minimum it may be greater than 11 billion USD. Many new social and medical services will be necessary to meet this challenge such that 60 million additional care workers will be needed [35–37]. These projections do not consider that all cases of dementia may not have been identified and diagnosed at this time [38, 39].

Cognitive loss impacts a large spectrum of the population. Dementia in the United States affects greater than 5 million people [4]. Many of these cases, 60 percent, are diagnosed as AD [4, 6, 17, 40–43]. Case of AD that are familial in origin comprise under 2% of all cases [4]. In familial AD that affects 200 families worldwide, mutations in the presenilin 1 or 2 genes occurs and an autosomal dominant mutated amyloid precursor protein (APP) gene exists. In these familial AD patients, illness can present prior to 55 years of age [44–46]. Familial AD can be the result of mutations in chromosome 21 leading to changes in APP, mutations in chromosome 14 causing changes in presenilin 1, and mutations in chromosomes 1, 14, and 21 such that mutations in chromosome 1 lead to changes in presenilin. However, it is the sporadic version of AD that leads to illness in patients over age 65 and represents the cases of AD in ten percent of the population in the world. The ε4 allele of the apolipoprotein E (APOE) gene represents an additional risk of developing AD in the sporadic group.

3. Biological clocks and circadian rhythm pathways for dementia treatment

Current attempts to treat dementia such as with cholinesterase inhibitors may lead to a decrease in the presenting symptoms but ultimately do not block the progression of the disease, such as in AD [27, 45, 47, 48]. Other treatments for cognitive loss can focus on metabolic disorders, such as diabetes mellitus (DM) [1, 20, 27, 41, 49, 50], and on vascular disease [19, 45, 51–53]. Yet, there exist other risks for developing vascular cognitive loss that can affect the efficacy of treatments such as tobacco use, alcohol consumption, hypertension, and a low level of education [20, 39, 54–57]. With reference to metabolic
disease, tight glucose control in the serum in combination with early diagnosis of DM may assist to limit the progression of the disease, but complications from DM can still ensue [6, 58–69]. Given the need for novel strategies directed against memory loss and dementia, exciting new avenues of development are now focusing upon biological clock mechanisms and include the pathways of the mechanistic target of rapamycin (mTOR), its associated pathways of mTOR Complex 1 (mTORC1), mTOR Complex 2 (mTORC2), the silent mating type information regulation 2 homolog 1 (Saccharomyces cerevisiae) (SIRT1), mammalian forkhead transcription factors (FoxOs), the growth factor erythropoietin (EPO), and the wingless pathway of Wnt pathway (Fig. 1).

Biological clocks and circadian rhythm pathways are vital components in the onset of nervous system disorders, memory loss, and dementia [6, 34, 39, 70–76] (Table 1). Changes in the function of biological clock pathways can impact cellular metabolic homeostasis [6, 76–85], cancer [6, 80, 81, 84, 86–89], energy metabolism and aging [70, 74, 77, 84, 90], mitochondrial energy maintenance [76, 81, 91, 92], renal disease [78, 86], and viral diseases [72, 93–101]. Circadian rhythm in mammals is controlled in a region over the optic chiasm that detects light with retinal photosensitive ganglion cells in the suprachiasmatic nucleus (SCN) [6, 84, 98]. With the exposure to external light, biological clock genes oversee biochemical cell transmissions, physiological process in the body, and changes in behavior. The SCN controls the temperature of the body, cortisol and melatonin release, and oxidative stress responses through a connected system among the hypothalamic nuclei, pineal gland, and vasoactive intestinal peptide [88, 102, 103]. As part of the biological clock gene group, members of the basic helix-loop-helix-PAS (Period-Arnt-Single-minded) transcription factor family, that include CLOCK and BMAL1 [104], control gene expression of Cryptochrome (Cry1 and Cry2) and Period (Per1, Per2, and Per3) [6, 78, 84, 86, 105–107]. Modulation of these pathways and auto-feedback interactions are controlled by PER:CRY heterodimers that block transcription during nuclear translocation promoted by CLOCK:BMAL1 complexes. Other regulatory pathways that can be activated by CLOCK:BMAL1 heterodimers include RORα and retinoic acid-related orphan receptors REV-ERBα, also termed NR1D1 (nuclear receptor subfamily 1, group D, member 1). The REV-ERBα and RORα receptors attach to retinoic acid-related orphan receptor response elements (ROREs) that exist in the BMAL1 promoter to block and promote rhythmic transcription of BMAL1 by RORs and REV-ERBs, respectively. REV-ERBs can inhibit transcription to lead to circadian oscillation of BMAL1 [74, 105].

With neurodegeneration and aging studies, experimental studies with Parkinson’s disease (PD) using 6-hydroxydopamine (6-OHDA) during chronic treatment with levodopa show depressed levels of BMAL1 and RORα, indicating that memory loss in PD patients also may be a result of medication that alters circadian rhythm clock genes [106]. Cognitive impairment with memory loss and neuronal injury may occur as a result of sleep fragmentation during extended space flight which alters circadian rhythm [108, 109]. Changes in the DNA methylation of biological clock genes may foster memory loss and changes in behavior since rhythmic methylation of BMAL1 has been shown in the brains of individuals with AD [70]. In experimental studies AD using mice, significant alterations have been observed in RNA clock gene expression that may suggest a dysfunction in the clock pathways during cognitive loss [110].
4. Circadian rhythm disruption and the wingless wnt pathway

Lifespan can be affected by biological clock genes. Lifespan in *Drosophila melanogaster* is decreased through three arrhythmic mutants involving ClkAR, cyc0 and tim0. In addition, mutations in ClkAR with increasing age can result in dysfunction with ambulation. Through the promotion of Clk function, the locomotor deficits in *Drosophila* were reversed. This loss of function appears linked to the absence of dopaminergic neurons instead of insults from oxidative stress [75]. Other studies in *Drosophila* also suggest negative effects with alterations in circadian rhythm [6, 80, 84] (Table 1). For example, TIMELESS, a mammalian homolog of *Drosophila* circadian rhythm gene, can lead to cell death and has increased expression in nasopharyngeal carcinoma. During increased TIMELESS expression, cell growth pathways are fostered that involve the wingless pathway of Wnt/β-catenin and resistance against chemotherapy to lead to cell apoptosis, such as with cisplatin, is increased [89]. Wnt proteins are cysteine-rich glycosylated proteins that can affect development of neurons, immune system function, tissue fibrosis, angiogenesis, stem cell development, and cancer [111–114]. Yet, detrimental effects with Wnt pathways can result to promote increased vascular growth of tumors [111, 115, 116] and tumorigenesis [40, 117–121]. As a result, these mechanisms may work in conjunction with TIMELESS. There also is evidence for sleep fragmentation and disruption of biological clock genes with shift work to indicate that these lighting and international travel are other examples that can lead to circadian rhythm disturbance [79]. Sleep deprivation affects circadian rhythm and can prevent the clearance of Aβ, α-synuclein, and tau that are tied to the progression of nervous system disorders that include AD and PD [34, 109]. Some work suggests that female healthcare workers with extended night shift work may be at enhanced risk for breast cancer [122]. The circadian gene *hClock* during increased expression also can lead to cancer and colorectal cancer metastatic disease through promotion genes that activate angiogenesis [123].

5. The mechanistic target of rapamycin (mTOR) and autophagy

Circadian clock genes rely upon pathways of both autophagy and the mechanistic target of rapamycin (mTOR) [6, 84, 124–126] (Table 1). Circadian rhythm dysfunction can lead to changes in the induction of autophagy especially during cognitive loss [72, 81, 84, 92, 127–129]. Autophagy plays a vital role in multiple diseases of the nervous system and can sequester and remove intracellular deposits during AD [19, 41, 130, 131], amyotrophic lateral sclerosis [48, 132, 133], Huntington’s disease (HD) [19, 134], traumatic brain injury [135–137], and PD [83, 130, 135, 138–140]. This removal of toxic intracellular substances may be important to maintain memory and cognition. As part of a programmed cell death pathway, autophagy is tied to oxidative stress [2, 29, 66, 67, 71, 141–145]. Autophagy pathways can recycle cytoplasmic organelles and components for tissue remodeling [19, 146] and can eliminate non-functional organelles [6, 71, 142, 147]. Macroautophagy reuses organelles in cells and packages cytoplasmic proteins into cellular components termed autophagosomes. Once associated with lysosomes, the autophagosomes are degraded to begin another process for the recycling of organelles [19]. Microautophagy promotes invagination of lysosomal membranes to allow for the digestion of cell cytoplasm.
components. Chaperone-mediated autophagy employs cytosolic chaperones to transport cytoplasmic cell components across lysosomal membranes.

Previous studies also suggest in experimental studies with AD that a baseline cyclic circadian rhythm that controls autophagy is necessary to reduce Aβ deposition and prevent memory loss [129, 148]. Alterations in environmental homeostasis [82, 129, 149] can alter circadian rhythm that results in loss of cognitive ability [2, 19, 49, 50, 84, 150]. Sleep fragmentation also can produce changes in hippocampal autophagy proteins and decrease memory function [4, 127, 151–154]. Cellular protection is dependent on the activation of autophagy with circadian clock proteins during insults with stroke, since loss in the function of the PER1 circadian clock protein can increase cerebral ischemia [128].

In regard to the mTOR pathway, mTOR is a 289-kDa serine/threonine protein kinase and is vital during nervous system disease and memory loss [2, 19, 20, 25, 49, 155–157]. mTOR is also known as the mammalian target of rapamycin and the FK506-binding protein 12-rapamycin complex-associated protein 1 [19, 85, 158, 159]. mTOR is the main component of the protein complexes mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2) [160–162]. mTORC1 and mTORC2 are then divided into additional components [2, 107, 163–165]. mTORC1 is composed of Raptor, Deptor (DEP domain-containing mTOR interacting protein), the proline rich Akt substrate 40 kDa (PRAS40), and mammalian lethal with Sec13 protein 8, termed mLST8 (mLST8) [20, 40, 166]. mTORC1 activity is controlled through a number of pathways that includes PRAS40 by blocking the association of p70 ribosomal S6 kinase (p70S6K) and the eukaryotic initiation factor 4E (eIF4E)-binding protein 1 (4EBP1) with Raptor [167, 168]. Rapamycin is an agent that can inhibit mTOR activity [164, 169–172]. Rapamycin blocks the activity of mTORC1 through its association with immunophilin FK-506-binding protein 12 (FKBP12) that attaches to the FKBP12 -rapamycin-binding domain (FRB) at the carboxy (C) -terminal of mTOR to impede the FRB domain of mTORC1 [4]. mTORC2 is composed of Rictor, Deptor, mLST8, the mammalian stress-activated protein kinase interacting protein (mSIN1), and the protein observed with Rictor-1 (Protor-1) [167, 173, 174]. mTORC2 oversees remodeling of the cytoskeleton through PKCα and the migration of cells through the Rac guanine nucleotide exchange factors P-Rex1 and P-Rex2 and through Rho signaling [175]. Cognitive decline can be associated with the loss of mTOR activity and altered circadian rhythm during extended space flight [108]. Ischemia in the brain that leads to stroke may be altered by alteration in circadian rhythm genes and fluctuations in the activity of mTOR [124, 128]. Other studies suggest that the absence of period2 (PER2), a mammalian circadian clock protein, can increase mTOR activity and chemotherapy drug resistance [125].

mTOR also maintains a relationship with the silent mating type information regulation 2 homolog 1 (Saccharomyces cerevisiae) (SIRT1). SIRT1 maintains an inverse relationship with mTOR [19, 176–180]. SIRT1 can also affect pathways of autophagy [49, 65, 163, 178, 181–186]. SIRT1 activity can lead to the expansion of neurites and promote the survival of neurons during conditions that limit nutrients that involves mTOR inhibition [187]. SIRT1 can foster growth of tumors during autophagy induction that requires the blockade of mTOR, indicating that autophagy and SIRT1 can be targeted to control tumorigenesis [183]. SIRT1 is necessary to foster autophagy and mTOR inhibition during oxidative stress.
to preserve mitochondrial function in embryonic stem cells [188]. During periods of elevated serum glucose, SIRT1 can block mTOR to offer vascular cell protection [189]. SIRT1 with the blockade of mTOR activity can increase photoreceptor cell survival [177] and limit cell senescence [190]. It is also important to note that some pathways that lead to nerve cell injury require a relationship between mTOR and SIRT1 that is symbiotic. During the loss of dopaminergic neuronal cells, it has been observed that a balance in activities of SIRT1, mTOR, and forkhead transcription factors are required to promote neuronal cell survival [191]. It also has been demonstrated that SIRT1 and mTOR absence during obesity can suppress core circadian components CLOCK and BMAL1 and lead to loss of metabolic cellular homeostasis. The agent metformin, an inhibitor of mTOR activity [4, 65, 72], can prevent such processes during obesity in experimental mouse models and can reverse the loss of SIRT1 function during inhibition of the circadian components CLOCK and BMAL1 [192].

6. The silent mating type information regulation 2 homolog 1 (Saccharomyces cerevisiae) (SIRT1)

Biological clock pathways closely rely upon SIRT1 [6, 84, 85, 91, 193, 194] (Table 1). SIRT1 is a histone deacetylase that can transfer acetyl groups from ε-N-acetyl lysine amino acids to the histones of deoxyribonucleic acid (DNA) to control transcription [19, 45, 48, 84, 85, 152, 195–200]. As noted above, SIRT1 plays a critical role in nervous system diseases [164, 199, 201, 202] that also are dependent upon autophagy regulation [113, 178, 185, 186, 190, 203]. Other work focuses on SIRT1 to control the expression of clock genes through PER2 deacetylation [204]. SIRT1 its ability to control multiple biological clock gene pathways indicates that loss of SIRT can impact circadian rhythm cycles and result in memory loss and AD [110].

Through SIRT1 pathways, the coenzyme β-nicotinamide adenine dinucleotide (NAD⁺) has an important function with clock genes that is linked to mTOR [20, 66, 72, 192, 205]. Control of circadian rhythm by SIRT1 and melatonin can impact glucose tolerance in cells [102]. Dementia onset can be dependent upon melatonin, a pineal hormone that controls circadian rhythm [81, 88, 95], as well as mTOR through autophagy induction [90, 206]. During the process of aging, circadian rhythm cycles involving melatonin can affect infection with coronavirus disease of 2019 (COVID-19) [94], cellular metabolism [90, 103], mitochondrial dysfunction [81], oxidative stress [207, 208], and inflammatory mediators [206, 209]. In addition, SIRT1 can affect biological clock rhythm through stem cell function [210] and inflammation during obesity [91] and neurodegeneration [209]. Cellular NAD⁺ pools fluctuate with circadian rhythmicity and with aging [72]. SIRT1 in connection with CLOCK:BMAL1 can control the circadian expression of nicotinamide phosphoribosyltransferase (NAMPT) that is required for NAD⁺ production. SIRT1 also through the NAMPT promoter can promote the circadian synthesis of its own coenzyme [211]. Yet, NAD⁺ cellular pools can become depleted during impairment of mitochondrial function to result in cell injury with cellular NAD⁺ pools oscillating with free nicotinamide levels and promoting cell injury, metabolic dysfunction, and loss of cognitive function [205].
SIRT1 regulation of biological clock genes also can affect cognitive function though growth factors, such as EPO [161, 197, 212–214]. The EPO gene is present on chromosome 7 and represents a single copy in a 5.4 kb region of the genomic DNA [215, 216]. The gene encodes for a polypeptide chain protein that has 193 amino acids [64, 217]. EPO later undergoes the removal of a carboxy-terminal arginine\textsuperscript{166} in the mature human and recombinant human EPO (rhEPO). A protein with a molecular weight of 30.4 kDa and 165 amino acids is generated as the mature protein [218–221]. EPO expression occurs in the brain, uterus, and liver [64, 161, 164, 215, 216, 222, 223], but the principal site for the production and secretion of EPO is the peritubular interstitial cells of the kidney [216, 217, 224–227]. It is important to note that expression of EPO is overseen by oxygen tension changes and not by the concentration of red blood cells [64, 228, 229].

In relation to SIRT1, EPO prevents metabolic dysfunction by modulating adipose energy homeostasis in adipocytes through the combined activation of peroxisome proliferator-activated receptor-\(\alpha\) (PPAR-\(\alpha\)) and SIRT1 [213] (Table 1). EPO promotes vascular cell protection in the brain through SIRT1 nuclear subcellular trafficking and blocks mitochondrial depolarization, cytochrome c release, BCL2 associated agonist of cell death (Bad) activity, and caspase activation [212]. EPO can increase human cardiomyocyte survival through SIRT1 activation during chemotherapy toxicity [197] and prevent brain neuronal cell loss through the up-regulation of SIRT1 [214]. EPO can block memory loss during AD [5, 43], control metabolic pathways [230, 231], and block mitochondrial dysfunction [197, 216, 222, 232–234]. However, control of biological clock gene pathways appear to be necessary for EPO and SIRT1 to offer cellular protection. Some studies indicate that during hypoxia specific clock genes, that include BMAL1 and PER2, are required for the production of EPO [235].

EPO also relies upon mTOR to affect cellular survival. EPO employs mTOR to foster neuronal regeneration through autophagy and apoptotic pathways [20, 203, 236–239]. EPO prevents apoptosis during A\(\beta\) exposure with mTOR activation to prevent caspase activation [240]. EPO can increase the survival of microglia during oxidative stress through mTOR signaling pathways [241]. EPO oversees mTOR, protein kinase B (Akt) [232, 242, 243], and proline rich Akt substrate 40 kDa (PRAS40) to promote the survival of neurons during oxygen-glucose deprivation [244].

### 7. Mammalian forkhead transcription factors (FoxOs)

Mammalian FOXO proteins of the O class are transcription factors and play a significant role in the nervous system. FoxO family members include FOXO1, FOXO3, FOXO4, and FOXO6 [67, 164, 245–247] (Table 1). FoxO proteins bind to deoxyribonucleic acid (DNA) through the FoxO-recognized element in the C-terminal basic region of the forkhead DNA binding domain. With the binding to DNA by FoxOs, target gene expression is blocked or promoted through fourteen protein-DNA contacts with the primary recognition site located at \(\alpha\)-helix H3. Phosphorylation or acetylation of FoxOs can change the binding of the C-terminal basic region to DNA to inhibit FoxO transcriptional activity [48, 152, 199, 248]. FoxOs are intimately connected circadian rhythm since they are linked to SIRT1 [4, 34, 48, 85, 248–252]. For example, insulin-phosphatidylinositol 3-kinase (PI3K) signaling...
that occurs in the liver is overseen by FoxO3 control of circadian rhythmicity through modulation of Clock. Loss of FoxO3 impairs the circadian amplitude and rhythmicity [253]. Autophagy induction also is dependent on mammalian FOXO proteins of the O class [12, 164, 202, 254, 255]. FoxO1 transcription factors [256] oversee the myelination of nerves that requires oligodendrocyte progenitor cells and determine the progression of disorders that include multiple sclerosis [257]. Additional studies indicate that epigenetic changes in DNA methylation and genetic variations of FoxO3a and FoxO1 also can affect demyelinating disorders [258]. Yet, it is important to state that a fine balance in FoxO activity is necessary to lead to the protection of cells since activation of FoxOs with autophagy can be beneficial. Sequestering and clearance of detrimental intracellular accumulations by FoxOs and autophagy can lead to increased survival of neurons [246, 259, 260].

In regard to SIRT1, blockade of the activity of FoxOs by SIRT1 can promote cell survival [19, 67, 249–251]. However, FoxOs can attach to the SIRT1 promoter region to further change forkhead transcription [181]. This mechanism permits FoxOs to use auto-feedback mechanisms to regulate the activity of SIRT1. FoxO proteins, including FoxO1, can oversee SIRT1 transcription and increase the expression of SIRT1 [261]. These studies suggest an intimate relationship between SIRT1 and FoxOs. Interestingly, SIRT1 and FoxOs can synergistically increase cell survival. SIRT1 and FoxO3a can work in unison to block memory loss and Aβ brain toxicity, mitochondrial dysfunction, and oxidative stress [5, 152, 262, 263].

8. Future perspectives

Neurodegenerative disorders that involve cognitive loss and dementia impact a significant proportion of the world’s population and lead to a large financial burden for all nations. Adding to these concerns is the knowledge that cognitive disorders present almost insurmountable challenges for treatment since they are multifactorial in origin and can result from multiple pathways that involve Aβ, tau, metabotropic receptors, excitotoxicity, lipid dysfunction, mitochondrial damage, astrocyte injury, loss of access to bright light, heavy metal disease, acetylcholine loss, oxidative stress, and metabolic dysfunction that involves DM. Novel new therapeutic strategies are desperately warranted. New investigations may meet this need with work that highlights biological clock genes that oversee circadian rhythm and involve the pathways of mTOR, SIRT1, FoxOs, EPO, and the Wnt/β-catenin pathway (Fig. 1). These pathways are complex in nature and intimately tied to autophagy induction that can sequester intracellular accumulations and potentially reduce cognitive loss under some conditions. Dysfunctional changes in biological clock genes and circadian rhythm can result in motor deficits, memory impairment, and the progression of dementia. Even chronic treatment regimens that occur during PD can alter circadian rhythm function and foster dementia. The pathways of autophagy may be one mechanism to oversee circadian rhythm homeostasis that can become lost during conditions of chronic sleep fragmentation.

The pathways that impact circadian rhythm have an intricate relationship that can lead to both beneficial as well as detrimental clinical effects. For example, blockade of mTOR
activity can change circadian rhythm, affect memory function, and increase neuronal cell injury such as during stroke. SIRT1 can oversee the production of NAD$^+$ pools that have been tied to circadian rhythmicity and if these cellular pools become depleted, cell injury and metabolic dysfunction can ensue with cognitive loss. Furthermore, without circadian rhythm control, the protective capability of EPO and SIRT1 may become absent and lead to mitochondrial dysfunction and the loss of cognition. In regard to FoxOs, SIRT1 and FoxOs may be required to work in unison to limit cognitive loss, mitochondrial dysfunction, and oxidative stress. Yet, it is important to remember that Wnt pathways that function in conjunction with circadian clock gene pathways, such as TIMELESS, may promote new angiogenesis and tumorigenesis. In addition, other circadian genes that include $b$Clock also may promote metastatic colorectal cancer through the promotion of angiogenesis-related gene activity and vascular cell growth.

These observations serve to form a strong foundation for the further investigation of biological clock genes and circadian rhythm in regards to their significant role in neurodegenerative disorders such as dementia. The circadian pathways involving mTOR, SIRT1, FoxOs, EPO, and the Wnt can offer considerable potential for the understanding and treatment of memory loss and neurodegenerative disorders. Yet, it is the intimate and complex relationship among these pathways that is most intriguing and potentially offers the greatest insight to harness this knowledge for the innovative treatment of dementia.

**Acknowledgment**

We appreciate the reviewers for their opinions and suggestions.

11. **Funding**

This research was supported by the following grants to Kenneth Maiese: American Diabetes Association, American Heart Association, NIH NIEHS, NIH NIA, NIH NINDS, NS053956, and NIH ARRA.

**Abbreviations:**

- AD: Alzheimer’s disease
- DM: diabetes mellitus
- EPO: erythropoietin
- FoxOs: mammalian forkhead transcription factors
- HD: Huntington’s disease
- NCDs: non-communicable diseases
- mTOR: the mechanistic target of rapamycin
- mTORC1: mTOR Complex 1
- mTORC2: mTOR Complex 2
- PER2: period2
**PRAS40**
proline rich Akt substrate 40 kDa

**SIRT1**
the silent mating type information regulation 2 homolog 1
(\textit{Saccharomyces cerevisiae})

**US**
United States

**USD**
United States Dollars

**Wnt**
\textit{wingless}

## 14. References

[1]. Engin AB, Engin A. Alzheimer’s Disease and Protein Kinases. Advances in Experimental Medicine and Biology 2021; 1275: 285–321. [PubMed: 33539020]

[2]. Perluigi M, Di Domenico F, Barone E, Butterfield DA. MTOR in Alzheimer disease and its earlier stages: Links to oxidative damage in the progression of this dementing disorder. Free Radical Biology and Medicine 2021; 169: 382–396. [PubMed: 33933601]

[3]. Su LD, Wang N, Han J, Shen Y. Group 1 Metabotropic Glutamate Receptors in Neurological and Psychiatric Diseases: Mechanisms and Prospective. Neuroscientist 2021. (in press)

[4]. Maiese K Taking aim at Alzheimer’s disease through the mammalian target of rapamycin. Annals of Medicine 2014; 46: 587–596. [PubMed: 25105207]

[5]. Maiese K Forkhead Transcription Factors: Formulating a FOXO Target for Cognitive Loss. Current Neurovascular Research 2017; 14: 415–420. [PubMed: 29149835]

[6]. Maiese K Cognitive impairment with diabetes mellitus and metabolic disease: innovative insights with the mechanistic target of rapamycin and circadian clock gene pathways. Expert Review of Clinical Pharmacology 2020; 13: 23–34. [PubMed: 31794280]

[7]. Caberlotto L, Nguyen T, Lauria M, Priami C, Rimondini R, Maioli S, et al. Cross-disease analysis of Alzheimer’s disease and type-2 Diabetes highlights the role of autophagy in the pathophysiology of two highly comorbid diseases. Scientific Reports 2019; 9: 3085. [PubMed: 30850634]

[8]. Cacabelos R, Carril JC, Cacabelos N, Kazantsev AG, Vostrov AV, Corzo L, et al. Sirtuins in Alzheimer’s Disease: SIRT2-Related GenoPhenotypes and Implications for PharmacoEpiGenetics. International Journal of Molecular Sciences 2019; 20: 1249.

[9]. Cai H, Li Y, Niringiyumukiza JD, Su P, Xiang W. Circular RNA involvement in aging: an emerging player with great potential. Mechanisms of Ageing and Development 2019; 178: 16–24. [PubMed: 30513309]

[10]. Chang R, Al Maghribi A, Vanderpoel V, Vasilevko V, Cribbs DH, Boado R, et al. Brain Penetrating Bifunctional Erythropoietin-Transferrin Receptor Antibody Fusion Protein for Alzheimer’s Disease. Molecular Pharmaceutics 2018; 15: 4963–4973. [PubMed: 30252487]

[11]. Cheng J, North BJ, Zhang T, Dai X, Tao K, Guo J, et al. The emerging roles of protein homeostasis-governing pathways in Alzheimer’s disease. Aging Cell 2018; 17: e12801. [PubMed: 29992725]

[12]. Czubowicz K, Ješko H, Wencel P, Lukiw WJ, Strosznajder RP. The Role of Ceramide and Sphingosine-1-Phosphate in Alzheimer’s Disease and other Neurodegenerative Disorders. Molecular Neurobiology 2019; 56: 5436–5455. [PubMed: 30612333]

[13]. Duitama M, Vargas-López V, Casas Z, Albarracin SL, Sutachan JJ, Torres YP. TRP Channels Role in Pain Associated With Neurodegenerative Diseases. Frontiers in Neuroscience 2020; 14: 782. [PubMed: 32848557]

[14]. Gonzalo-Gobernado R, Peruchó J, Vallejo-Muñoz M, Casarejos MJ, Reimers D, Jiménez-Escrig A, et al. Liver Growth Factor "LGF" as a Therapeutic Agent for Alzheimer’s Disease. International Journal of Molecular Sciences 2020; 21: 9201.
[15]. Hao Y, Guo M, Feng Y, Dong Q, Cui M. Lysophospholipids and Their G-Coupled Protein Signaling in Alzheimer’s Disease: From Physiological Performance to Pathological Impairment. Frontiers in Molecular Neuroscience 2020; 13: 58. [PubMed: 32351364]

[16]. Huang C, Wen C, Yang M, Li A, Fan C, Gan D, et al. Astaxanthin Improved the Cognitive Deficits in APP/PS1 Transgenic Mice via Selective Activation of mTOR. Journal of Neuroimmune Pharmacology 2021; 16: 609–619. [PubMed: 32944864]

[17]. Khan H, Tundis R, Ullah H, Aschner M, Belwal T, Mirzaei H, et al. Flavonoids targeting NRF2 in neurodegenerative disorders. Food and Chemical Toxicology 2020; 146: 111817. [PubMed: 33069760]

[18]. Li X, Li K, Chu F, Huang J, Yang Z. Graphene oxide enhances β-amyloid clearance by inducing autophagy of microglia and neurons. Chemico-Biological Interactions 2020; 325: 109126. [PubMed: 32430275]

[19]. Maiase K The mechanistic target of rapamycin (mTOR) and the silent mating-type information regulation 2 homolog 1 (SIRT1): oversight for neurodegenerative disorders. Biochemical Society Transactions 2018; 46: 351–360. [PubMed: 29523769]

[20]. Maiase K Dysregulation of metabolic flexibility: the impact of mTOR on autophagy in neurodegenerative disease. International Review of Neurobiology 2020; 155: 1–35. [PubMed: 32854851]

[21]. Maiase K, Chong ZZ, Wang S, Shang YC. Oxidant stress and signal transduction in the nervous system with the PI 3-K, Akt, and mTOR cascade. International Journal of Molecular Sciences 2013; 13: 13830–13866.

[22]. Prokopenko D, Hecker J, Kirchner R, Chapman BA, Hoffman O, Mullin K, et al. Identification of Novel Alzheimer’s Disease Loci Using Sex-Specific Family-Based Association Analysis of whole-Genome Sequence Data. Scientific Reports 2020; 10: 5029. [PubMed: 32193444]

[23]. Sánchez-Melgar A, Albasan JL, Pallás M, Martín M. Resveratrol Differently Modulates Group I Metabotropic Glutamate Receptors Depending on Age in SAMP8 Mice. ACS Chemical Neuroscience 2020; 11: 1770–1780. [PubMed: 32437602]

[24]. Sedighi M, Baluchnejadmojarad T, Afshin-Majd S, Amiri M, Aminzade M, Roghani M. Anti-aging Klotho Protects SH-SY5Y Cells against Amyloid β1–42 Neurotoxicity: Involvement of Wnt1/pCREB/Nrf2/HO-1 Signaling. Journal of Molecular Neuroscience 2021; 71: 19–27. [PubMed: 32627121]

[25]. Wang H, Li Q, Sun S, Chen S. Neuroprotective Effects of Salidroside in a Mouse Model of Alzheimer’s Disease. Cellular and Molecular Neurobiology 2020; 40: 1133–1142. [PubMed: 32002777]

[26]. Wang Y, Lin Y, Wang L, Zhan H, Luo X, Zeng Y, et al. TREM2 ameliorates neuroinflammatory response and cognitive impairment via PI3K/AKT/FoxO3a signaling pathway in Alzheimer’s disease mice. Aging 2020; 12: :20862–20879. [PubMed: 33065533]

[27]. Hu Z, Jiao R, Wang P, Zhu Y, Zhao J, De Jager P, et al. Shared Causal Paths underlying Alzheimer’s dementia and Type 2 Diabetes. Scientific Reports 2020; 10: 4107. [PubMed: 32139775]

[28]. Zhang W, Bai S, Yang J, Zhang Y, Liu Y, Nie J, et al. FoxO1 overexpression reduces Aβ production and tau phosphorylation in vitro. Neuroscience Letters 2020; 738: 135322. [PubMed: 32860886]

[29]. Fang Y, Lu L, Liang Y, Peng D, Aschner M, Jiang Y. Signal transduction associated with lead-induced neurological disorders: a review. Food and Chemical Toxicology 2021; 150: 112063. [PubMed: 33596455]

[30]. Roccaro I, Smirni D. Fiat Lux: the Light became Therapy. An Overview on the Bright Light Therapy in Alzheimer’s Disease Sleep Disorders. Journal of Alzheimer’S Disease 2020; 77: 113–125.

[31]. Burillo J, Marqués P, Jiménez B, González-Blanco C, Benito M, Guillén C. Insulin Resistance and Diabetes Mellitus in Alzheimer’s Disease. Cells 2021; 10: 1236. [PubMed: 34069890]

[32]. Querfurth H, Lee H. Mammalian/mechanistic target of rapamycin (mTOR) complexes in neurodegeneration. Molecular Neurodegeneration 2021; 16: 44. [PubMed: 34215308]
[33]. Schell M, Wardelmann K, Kleinridders A. Untangling the effect of insulin action on brain mitochondria and metabolism. Journal of Neuroendocrinology 2021; 33: e12932. [PubMed: 33506556]

[34]. Maiese K Cognitive Impairment and Dementia: Gaining Insight through Circadian Clock Gene Pathways. Biomolecules 2021; 11: 1–18.

[35]. World Health Organization. Description of the global burden of NCDs, their risk factors and determinants. Global Status Report On Noncommunicable Diseases 2010 Geneva: World Health Organization. 2011; 1–176.

[36]. World Health Organization. Dementia: A public health priority Geneva: World Health Organization. 2012; 1–4.

[37]. World Health Organization. Global action plan on the public health response to dementia 2017–2025 Geneva: World Health Organization. 2017; 1–44.

[38]. Maiese K MicroRNAs for the Treatment of Dementia and Alzheimer’s Disease. Current Neurovascular Research 2019; 16: 1–2. [PubMed: 30732557]

[39]. Maiese K Impacting dementia and cognitive loss with innovative strategies: mechanistic target of rapamycin, clock genes, circular non-coding ribonucleic acids, and Rho/Rock. Neural Regeneration Research 2019; 14: 773–774. [PubMed: 30688262]

[40]. Maiese K, Chong ZZ, Shang YC, Wang S. MTOR: on target for novel therapeutic strategies in the nervous system. Trends in Molecular Medicine 2013; 19: 51–60. [PubMed: 23265840]

[41]. Hsieh C, Liu C, Lee C, Yu L, Wang J. Acute glucose fluctuation impacts microglial activity, leading to inflammatory activation or self-degradation. Scientific Reports 2019; 9: 840. [PubMed: 3069689]

[42]. Kowalska M, Pickut T, Prendecki M, Sodel A, Kozubski W, Dorszewska J. Mitochondrial and Nuclear DNA Oxidative Damage in Physiological and Pathological Aging. DNA and Cell Biology 2020; 39: 1410–1420. [PubMed: 32315547]

[43]. Sun J, Martin JM, Vanderpoel V, Sumbria RK. The Promises and Challenges of Erythropoietin for Treatment of Alzheimer’s Disease. NeuroMolecular Medicine 2019; 21: 12–24. [PubMed: 30656553]

[44]. Agis-Torres A, Söllhuber M, Fernandez M, Sanchez-Montero JM. Multi-Target-Directed Ligands and other Therapeutic Strategies in the Search of a Real Solution for Alzheimer’s Disease. Current Neuropharmacology 2014; 12: 2–36. [PubMed: 24533013]

[45]. Maiese K Sirtuins: Developing Innovative Treatments for Aged-Related Memory Loss and Alzheimer’s Disease. Current Neurovascular Research 2018; 15: 367–371. [PubMed: 30484407]

[46]. Maiese K Addressing Alzheimer’s Disease and Cognitive Loss through Autophagy. Current Neurovascular Research 2020; 17: 339–341. [PubMed: 32693767]

[47]. Cheng X, Song C, Du Y, Gaur U, Yang M. Pharmacological Treatment of Alzheimer’s Disease: Insights from Drosophila melanogaster. International Journal of Molecular Sciences 2020; 21: 4621.

[48]. Maiese K FoxO proteins in the nervous system. Analytical Cellular Pathology 2015; 2015: 569392.

[49]. Maiese K Novel nervous and multi-system regenerative therapeutic strategies for diabetes mellitus with mTOR. Neural Regeneration Research 2016; 11: 372–385. [PubMed: 27127460]

[50]. Su M, Naderi K, Samson N, Youssef I, Fulop L, Bozso Z, et al. Mechanisms Associated with Type 2 Diabetes as a Risk Factor for Alzheimer-Related Pathology. Molecular Neurobiology 2019; 56: 5815–5834. [PubMed: 30684218]

[51]. Maiese K, Chong ZZ, Hou J, Shang YC. New strategies for Alzheimer’s disease and cognitive impairment. Oxidative Medicine and Cellular Longevity 2009; 2: 279–289. [PubMed: 20716915]

[52]. Wahl D, Solon-Biet SM, Cogger VC, Fontana L, Simpson SJ, Le Couteur DG, et al. Aging, lifestyle and dementia. Neurobiology of Disease 2019; 130: 104481. [PubMed: 31136814]

[53]. Chen F, Liu Z, Peng W, Gao Z, Ouyang H, Yan T, et al. Activation of EphA4 induced by EphrinA1 exacerbates disruption of the blood-brain barrier following cerebral ischemia-reperfusion via the Rho/ROCK signaling pathway. Experimental and Therapeutic Medicine 2018; 16: 2651–2658. [PubMed: 30186497]
[54]. Maiese K Alcohol Use Disorder and Dementia: Critical Mechanisms for Cognitive Loss. Current Neurovascular Research 2021; 18: 1–3. [PubMed: 33583379]

[55]. Bahorik A, Bobrow K, Hoang T, Yaffe K. Increased risk of dementia in older female US veterans with alcohol use disorder. Addiction 2021; 116: 2049–2055. [PubMed: 33449402]

[56]. Ong W, Wu Y, Farooqui T, Farooqui AA. Qi Fu Yin-a Ming Dynasty Prescription for the Treatment of Dementia. Molecular Neurobiology 2018; 55: 7389–7400. [PubMed: 29417476]

[57]. Xing W, Li D, Zhou Y, Song D, Wang X, Wang S, et al. Jidong cognitive impairment cohort study: objectives, design, and baseline screening. Neural Regeneration Research 2020; 15: 1111–1119. [PubMed: 31823892]

[58]. Coca SG, Ismail-Beigi F, Haq N, Krumholz HM, Parikh CR. Role of intensive glucose control in development of renal end points in type 2 diabetes mellitus: systematic review and meta-analysis of intensive glucose control in type 2 diabetes. Archives of Internal Medicine 2012; 172: 761–769. [PubMed: 22636820]

[59]. Barchetta I, Cimini FA, Ciccarelli G, Baroni MG, Cavallo MG. Sick fat: the good and the bad of old and new circulating markers of adipose tissue inflammation. Journal of Endocrinological Investigation 2019; 42: 1257–1272. [PubMed: 31073969]

[60]. Fan X, Zhao Z, Wang D, Xiao J. Glycogen synthase kinase-3 as a key regulator of cognitive function. Acta Biochimica et Biophysica Sinica 2020; 52: 219–230. [PubMed: 32147679]

[61]. Fernandez-Ruiz R, García-Alamán A, Esteban Y, Mir-Coll J, Serra-Navarro B, Fontcuberta-PiSunyer M, et al. Wisp1 is a circulating factor that stimulates proliferation of adult mouse and human beta cells. Nature Communications 2020; 11: 5982.

[62]. Januszewski AS, Watson CJ, O’Neill V, McDonald K, Ledwidge M, Robson T, et al. FKBPL is associated with metabolic parameters and is a novel determinant of cardiovascular disease. Scientific Reports 2020; 10: 21655. [PubMed: 3303872]

[63]. Liu C, Zhong C, Chen R, Zhou X, Wu J, Han J, et al. Higher dietary vitamin C intake is associated with a lower risk of gestational diabetes mellitus: a longitudinal cohort study. Clinical Nutrition 2020; 39: 198–203. [PubMed: 30773371]

[64]. Maiese K New Insights for Oxidative Stress and Diabetes Mellitus. Oxidative Medicine and Cellular Longevity 2015; 2015: 875961. [PubMed: 26064426]

[65]. Maiese K New Insights for nicotinamide: Metabolic disease, autophagy, and mTOR. Frontiers in Bioscience (Landmark edition) 2020; 25: 1925–1973. [PubMed: 32472766]

[66]. Maiese K Nicotinamide as a Foundation for Treating Neurodegenerative Disease and Metabolic Disorders. Current Neurovascular Research 2021. (in press)

[67]. Cronin P, McCarthy MJ, Lim ASP, Salmon DP, Galasko D, Masliah E, et al. Circadian alterations during early stages of Alzheimer’s disease are associated with aberrant cycles of DNA methylation in BMAL1. Alzheimer’s & Dementia 2017; 13: 689–700.

[68]. Klonowsky DJ, Abdel-Aziz AK, Abdelatif S, Abdellatif M, Abdoli A, Abel S, et al. Guidelines for the use and interpretation of assays for monitoring autophagy (4th edition). Autophagy 2021; 17: 1–382. [PubMed: 33634751]

[69]. Yamashima T, Ota T, Mizukoshi E, Nakamura H, Yamamoto Y, Kikuchi M, et al. Intake of ω-6 Polyunsaturated Fatty Acid-Rich Vegetable Oils and Risk of Lifestyle Diseases. Advances in Nutrition 2020; 11: 1489–1509. [PubMed: 32623461]

[70]. Maiese K Nicotinamide: Oversight of Metabolic Dysfunction through SIRT1, mTOR, and Clock Genes. Current Neurovascular Research 2020; 17: 765–783. [PubMed: 33183203]

[71]. Maiese K Nicotinamide: Oversight of Metabolic Dysfunction through SIRT1, mTOR, and Clock Genes. Current Neurovascular Research 2020; 17: 765–783. [PubMed: 33183203]

[72]. Maiese K Nicotinamide: Oversight of Metabolic Dysfunction through SIRT1, mTOR, and Clock Genes. Current Neurovascular Research 2020; 17: 765–783. [PubMed: 33183203]

[73]. Hardeland R Neuroprotection by radical avoidance: search for suitable agents. Molecules 2009; 14: 5054–5102. [PubMed: 20032877]
[74]. Hood S, Amir S. Neurodegeneration and the Circadian Clock. Frontiers in Aging Neuroscience 2017; 9: 170. [PubMed: 28611660]

[75]. Vaccaro A, Issa A, Seugnet L, Birman S, Klarsfeld A. Drosophila Clock is Required in Brain Pacemaker Neurons to Prevent Premature Locomotor Aging Independently of its Circadian Function. PLoS Genetics 2017; 13: e1006507. [PubMed: 28072817]

[76]. Zhang H, Liang J, Chen N. Do not neglect the role of circadian rhythm in muscle atrophy. Ageing Research Reviews 2020; 63: 101155. [PubMed: 32882420]

[77]. De Nobrega AK, Luz KV, Lyons LC. Resetting the Aging Clock: Implications for Managing Age-Related Diseases. Advances in Experimental Medicine and Biology 2020; 389: 193–265.

[78]. Egstrand S, Olgaard K, Lewin E. Circadian rhythms of mineral metabolism in chronic kidney disease-mineral bone disorder. Current Opinion in Nephrology & Hypertension 2020; 29: 367–377. [PubMed: 32452917]

[79]. Finger A, Kramer A. Mammalian circadian systems: Organization and modern life challenges. Acta Physiologica 2021; 231: e13548. [PubMed: 32846050]

[80]. Ma D, Hou L, Xia H, Li H, Fan H, Jia X, et al. PER2 inhibits proliferation and stemness of glioma stem cells via the Wnt/β-catenin signaling pathway. Oncology Reports 2020; 44: 533–542. [PubMed: 32468039]

[81]. Mocayar Marón FJ, Ferder L, Reiter RJ, Manucha W. Daily and seasonal mitochondrial protection: Unraveling common possible mechanisms involving vitamin D and melatonin. The Journal of Steroid Biochemistry and Molecular Biology 2020; 199: 105595. [PubMed: 31954766]

[82]. Qi X, Mitter SK, Yan Y, Busik JV, Grant MB, Boulton ME. Diurnal Rhythmicity of Autophagy Is Impaired in the Diabetic Retina. Cells 2020; 9: 905.

[83]. Tatullo M, Marcelli B, Zullo MJ, Codispoti B, Paduano F, Benincasa C, et al. Exosomes from Human Periapical Cyst-MSCs: Theranostic Application in Parkinson’s Disease. International Journal of Medical Sciences 2020; 17: 657–663. [PubMed: 32210716]

[84]. Maiese K Moving to the Rhythm with Clock (Circadian) Genes, Autophagy, mTOR, and SIRT1 in Degenerative Disease and Cancer. Current Neurovascular Research 2017; 14: 299–304. [PubMed: 28721811]

[85]. Maiese K Novel Treatment Strategies for the Nervous System: Circadian Clock Genes, Non-coding RNAs, and Forkhead Transcription Factors. Current Neurovascular Research 2018; 15: 81–91. [PubMed: 29557749]

[86]. Angelousi A, Kassi E, Ansari-Nasiri N, Randeva H, Kaltasas G, Chrousos G. Clock genes and cancer development in particular in endocrine tissues. Endocrine-Related Cancer 2019; 26: R305–R317. [PubMed: 30959483]

[87]. Zhang Y, Peng X, Yang H, Zhao H, Xia B, You Y. The expression of the circadian gene TIMELESS in non-small-cell lung cancer and its clinical significance. International Journal of Clinical and Experimental Pathology 2020; 13: 2297–2304. [PubMed: 33042334]

[88]. Bonmati-Carrion MA, Tomas-Loba A. Melatonin and Cancer: A Polyhedral Network Where the Source Matters. Antioxidants 2021; 10: 210. [PubMed: 33535472]

[89]. Liu SL, Lin HX, Lin CY, Sun XQ, Ye LP, Qiu F, et al. TIMELESS confers cisplatin resistance in nasopharyngeal carcinoma by activating the Wnt/β-catenin signaling pathway and promoting the epithelial mesenchymal transition. Cancer Letters 2017; 402: 117–130. [PubMed: 28583847]

[90]. Jenwitheesuk A, Nopparat C, Mukda S, Wongchitrat P, Govitrapong P. Melatonin regulates aging and neurodegeneration through energy metabolism, epigenetics, autophagy and circadian rhythm pathways. International Journal of Molecular Sciences 2014; 15: 16848–16884. [PubMed: 25247581]

[91]. Liu Z, Gan L, Zhang T, Ren Q, Sun C. Melatonin alleviates adipose inflammation through elevating alpha-ketoglutarate and diverting adipose-derived exosomes to macrophages in mice. Journal of Pineal Research 2018; 64: 12455.

[92]. Rossetti ML, Esser KA, Lee C, Tomko RJ, Eroshkin AM, Gordon BS. Disruptions to the limb muscle core molecular clock coincide with changes in mitochondrial quality control following androgen depletion. American Journal of Physiology-Endocrinology and Metabolism 2019; 317: E631–E645. [PubMed: 31361545]
[93]. Borrmann H, Davies R, Dickinson M, Pedroza-Pacheco I, Schilling M, Vaughan-Jackson A, et al. Pharmacological activation of the circadian component REV-ERB inhibits HIV-1 replication. Scientific Reports 2020; 10: 13271. [PubMed: 32764708]

[94]. Cardinali DP, Brown GM, Reiter RJ, Pandi-Perumal SR. Elderly as a High-risk Group during COVID-19 Pandemic: Effect of Circadian Misalignment, Sleep Dysregulation and Melatonin Administration. Sleep and Vigilance 2020; 4: 81–87.

[95]. Crespo I, Fernández-Palanca P, San-Miguel B, Álvez M, González-Gallego J, Tuñón MJ. Melatonin modulates mitophagy, innate immunity and circadian clocks in a model of viral-induced fulminant hepatic failure. Journal of Cellular and Molecular Medicine 2020; 24: 7625–7636. [PubMed: 32468679]

[96]. Lim RK, Wambier CG, Goren A. Are night shift workers at an increased risk for COVID-19? Medical Hypotheses 2020; 144: 110147. [PubMed: 32758906]

[97]. Mazzoccoli G, Vinciguerra M, Carbone A, Relógio A. The Circadian Clock, the Immune System, and Viral Infections: The Intricate Relationship Between Biological Time and Host-Virus Interaction. Pathogens 2020; 9: 83.

[98]. Maiese K Circadian Clock Genes: Targeting Innate Immunity for Antiviral Strategies Against COVID-19. Current Neurovascular Research 2020; 17: 531–533. [PubMed: 33272180]

[99]. Morin CM, Carrier J, Bastien C, Godbout R. Sleep and circadian rhythm in response to the COVID-19 pandemic. Canadian Journal of Public Health 2020; 111: 654–657. [PubMed: 32700231]

[100]. Tamimi F, Abusamak M, Akkanti B, Chen Z, Yoo S, Karmouty Quintana H. The case for chronotherapy in Covid-19-induced acute respiratory distress syndrome. British Journal of Pharmacology 2020; 177: 4845–4850. [PubMed: 32442317]

[101]. Mayes K The Mechanistic Target of Rapamycin (mTOR): Novel Considerations as an Antiviral Treatment. Current Neurovascular Research 2020; 17: 332–337. [PubMed: 32334502]

[102]. Hardeland R Melatonin and the pathologies of weakened or dysregulated circadian oscillators. Journal of Pineal Research 2017; 62: 12377.

[103]. Lin F, Chen Y, Li X, Zhao Q, Tan Z. Over-expression of circadian clock gene Bmal1 affects proliferation and the canonical Wnt pathway in NIH-3T3 cells. Cell Biochemistry and Function 2013; 31: 166–172. [PubMed: 22961668]

[104]. Bunney BG, Li JZ, Walsh DM, Stein R, Vawter MP, Cartagena P, et al. Circadian dysregulation of clock genes: clues to rapid treatments in major depressive disorder. Molecular Psychiatry 2015; 20: 48–55. [PubMed: 25349171]

[105]. Li S, Wang Y, Liu W, Lyu D, Wang F, Mao C, et al. Long-term Levodopa Treatment Accelerates the Circadian Rhythm Dysfunction in a 6-hydroxydopamine Rat Model of Parkinson’s Disease. Chinese Medical Journal 2017; 130: 1085–1092. [PubMed: 28469105]

[106]. Yu M, Zhang H, Wang B, Zhang Y, Zheng X, Shao B, et al. Key Signaling Pathways in Aging and Potential Interventions for Healthy Aging. Cells 2021; 10: 660. [PubMed: 33809718]

[107]. Wu X, Li D, Liu J, Diao L, Ling S, Li Y, et al. Dammarane Sapogenins Ameliorates Neurocognitive Functional Impairment Induced by Simulated Long-Duration Spaceflight. Frontiers in Pharmacology 2017; 8: 315. [PubMed: 28611667]

[108]. Maiiese K Sleep Disorders, Neurodegeneration, Glymphatic Pathways, and Circadian Rhythm Disruption. Current Neurovascular Research. 2021. (in press)

[109]. Bellanti F, Iannelli G, Blonda M, Tamborra R, Villani R, Romano A, et al. Alterations of Clock Gene RNA Expression in Brain Regions of a Triple Transgenic Model of Alzheimer’s Disease. Journal of Alzheimer’s Disease 2017; 59: 615–631.

[110]. Maiiese K WISP1: Clinical Insights for a Proliferative and Restorative Member of the CCN Family. Current Neurovascular Research 2014; 11: 378–389. [PubMed: 25219658]

[111]. Maiiese K The bright side of reactive oxygen species: lifespan extension without cellular demise. Journal of Translational Science 2016; 2: 185–187. [PubMed: 27200181]
[113]. Maiese K Prospects and Perspectives for WISP1 (CCN4) in Diabetes Mellitus. Current Neurovascular Research 2020; 17: 327–331. [PubMed: 32216738]

[114]. Maiese K, Li F, Chong ZZ, Shang YC. The Wnt signaling pathway: aging gracefully as a protectionist? Pharmacology & Therapeutics 2008; 118: 58–81. [PubMed: 18313758]

[115]. Chen X, Wang CC, Song SM, Wei SY, Li JS, Zhao SL, et al. The administration of erythropoietin attenuates kidney injury induced by ischemia/reperfusion with increased activation of Wnt/beta-catenin signaling. Journal of the Formosan Medical Association 2015; 114: 430–437. [PubMed: 25682558]

[116]. Chong ZZ, Shang YC, Maiese K. Cardiovascular disease and mTOR signaling. Trends in Cardiovascular Medicine 2011; 21: 151–155. [PubMed: 22732551]

[117]. Jia S, Qu T, Feng M, Ji K, Li Z, Jiang W, et al. Association of Wnt1-inducible signaling pathway protein-1 with the proliferation, migration and invasion in gastric cancer cells. Tumour Biology 2017; 39: 1010428317699755. [PubMed: 28618940]

[118]. Maiese K Stem cell guidance through the mechanistic target of rapamycin. World Journal of Stem Cells 2015; 7: 999–1009. [PubMed: 26328016]

[119]. Maiese K Non-coding RNAs: Cracking the Code for Clinical Disease. Current Neurovascular Research 2017; 14: 1–2. [PubMed: 27923342]

[120]. Tsai H, Tzeng H, Huang C, Huang Y, Tsai C, Wang S, et al. WISP-1 positively regulates angiogenesis by controlling VEGF-a expression in human osteosarcoma. Cell Death & Disease 2017; 8: e2750–e2750. [PubMed: 28406476]

[121]. Yang C, Ji S, Li Y, Fu L, Jiang T, Meng F. Beta-Catenin promotes cell proliferation, migration, and invasion but induces apoptosis in renal cell carcinoma. OncoTargets and Therapy 2017; 10: 711–724. [PubMed: 28260916]

[122]. Wegrzyn LR, Tamimi RM, Rosner BA, Brown SB, Stevens RG, Eliassen AH, et al. Rotating Night Shift Work and Risk of Breast Cancer in The Nurses’ Health Studies. American Journal of Epidemiology 2017; 186: 532–540. [PubMed: 28541391]

[123]. Wang Y, Sun N, Lu C, Bei Y, Qian R, Hua L. Upregulation of circadian gene 'hClock' contribution to metastasis of colorectal cancer. International Journal of Oncology 2017; 50: 2191–2199. [PubMed: 28498393]

[124]. Beker MC, Caglayan B, Yalcin E, Caglayan AB, Turkseven S, Gurel B, et al. Time-of-Day Dependent Neuronal Injury after Ischemic Stroke: Implication of Circadian Clock Transcriptional Factor Bmal1 and Survival Kinase AKT. Molecular Neurobiology 2018; 55: 2565–2576. [PubMed: 28421530]

[125]. Chen B, Tan Y, Li Y, Chen L, Wu S, et al. Per2 participates in AKT-mediated drug resistance in a549/DDP lung adenocarcinoma cells. Oncology Letters 2017; 13: 423–428. [PubMed: 28123577]

[126]. Ramanathan C, Kathale ND, Liu D, Lee C, Freeman DA, Hogenesch JB, et al. mTOR signaling regulates central and peripheral circadian clock function. PLoS Genetics 2018; 14: e1007369. [PubMed: 29750810]

[127]. He Y, Cornelissen-Guillaume GG, He J, Kastin AJ, Harrison LM, Pan W. Circadian rhythm of autophagy proteins in hippocampus is blunted by sleep fragmentation. Chronobiology International 2016; 33: 555–560. [PubMed: 27078501]

[128]. Rami A, Fekadu J, Rawasheh O. The Hippocampal Autophagic Machinery is Depressed in the Absence of the Circadian Clock Protein per1 that may Lead to Vulnerability during Cerebral Ischemia. Current Neurovascular Research 2017; 14: 207–214. [PubMed: 28625127]

[129]. Wang X, Xu Z, Cai Y, Zeng S, Peng B, Ren X, et al. Rheostatic Balance of Circadian Rhythm and Autophagy in Metabolism and Disease. Frontiers in Cell and Developmental Biology 2020; 24: 616434.

[130]. Zhang Y, Wu Q, Zhang L, Wang Q, Yang Z, Liu J, et al. Caffeic acid reduces A53T alpha-synuclein by activating JNK/Bcl-2-mediated autophagy in vitro and improves behaviour and protects dopaminergic neurons in a mouse model of Parkinson’s disease. Pharmacological Research 2019; 150: 104538. [PubMed: 31707034]

Front Biosci (Landmark Ed). Author manuscript; available in PMC 2022 January 13.
[131]. Zhou T, Zhuang J, Wang Z, Zhou Y, Li W, Wang Z, et al. Glaucocalyxin A as a natural product increases amyloid beta clearance and decreases tau phosphorylation involving the mammalian target of rapamycin signaling pathway. Neuroreport 2019; 30: 310–316. [PubMed: 30688759]
[132]. Francois A, Terro F, Quellard N, Fernandez B, Chassaing D, Janet T, et al. Impairment of autophagy in the central nervous system during lipopolysaccharide-induced inflammatory stress in mice. Molecular Brain 2014; 7: 56. [PubMed: 25169902]
[133]. Sullivan PM, Zhou X, Robins AM, Paushter DH, Kim D, Smolka MB, et al. The ALS/FTLD associated protein C9orf72 associates with SMCR8 and WDR41 to regulate the autophagy-lysosome pathway. Acta Neuropathologica Communications 2016; 4: 51. [PubMed: 27193190]
[134]. Lee J, Tecedor L, Chen Y, Monteys A, Sowada M, Thompson L, et al. Reinstating Aberrant mTORC1 Activity in Huntington’s Disease Mice Improves Disease Phenotypes. Neuron 2015; 85: 303–315. [PubMed: 25556834]
[135]. Maiese K Targeting molecules to medicine with mTOR, autophagy and neurodegenerative disorders. British Journal of Clinical Pharmacology 2016; 82: 1245–1266. [PubMed: 26469771]
[136]. Ye Y, Zhang P, Qian Y, Yin B, Yan M. The Effect of Pyrroloquinoline Quinone on the Expression of WISP1 in Traumatic Brain Injury. Stem Cells International 2017; 2017: 1–16.
[137]. Zhang P, Ye Y, Qian Y, Yin B, Zhao J, Zhu S, et al. The Effect of Pyrroloquinoline Quinone on Apoptosis and Autophagy in Traumatic Brain Injury. CNS & Neurological Disorders Drug Targets 2017; 16: 724–736. [PubMed: 28124619]
[138]. Corti O, Blomgren K, Poletti A, Beart PM. Autophagy in neurodegeneration: New insights underpinning therapy for neurological diseases. Journal of Neurochemistry 2020; 154: 354–371. [PubMed: 32149395]
[139]. Fields CR, Bengoa-Vergniory N, Wade-Martins R. Targeting Alpha-Synuclein as a Therapy for Parkinson’s Disease. Frontiers in Molecular Neuroscience 2019; 12: 299. [PubMed: 31866823]
[140]. Zhou ZD, Selvaratnam T, Lee JCT, Chao YX, Tan E. Molecular targets for modulating the protein translation vital to proteostasis and neuron degeneration in Parkinson’s disease. Translational Neurodegeneration 2019; 8: 6. [PubMed: 30740222]
[141]. Jayaraj RL, Beiram R, Azimuthah S, Mf NM, Ojha SK, Adem A, et al. Valeric Acid Protects Dopaminergic Neurons by Suppressing Oxidative Stress, Neuroinflammation and Modulating Autophagy Pathways. International Journal of Molecular Sciences 2020; 21: 7670.
[142]. Maiese K, Chong ZZ, Shang YC, Wang S. Targeting disease through novel pathways of apoptosis and autophagy. Expert Opinion on Therapeutic Targets 2012; 16: 1203–1214. [PubMed: 22924465]
[143]. Wang H, Dou S, Zhu J, Shao Z, Wang C, Cheng B. Regulatory effects of ghrelin on endoplasmic reticulum stress, oxidative stress, and autophagy: Therapeutic potential. Neuropeptides 2021; 85: 102112. [PubMed: 33333485]
[144]. Xie T, Ye W, Liu J, Zhou L, Song Y. The Emerging Key Role of Klotho in the Hypothalamus-Pituitary-Ovarian Axis. Reproductive Sciences 2021; 28: 322–331. [PubMed: 32783104]
[145]. Zhou Q, Tang S, Zhang X, Chen L. Targeting PRAS40: a novel therapeutic strategy for human diseases. Journal of Drug Targeting 2021; 29: 703–715. [PubMed: 33504218]
[146]. Dorvash M, Farahmandnia M, Tavassoly I. A Systems Biology Roadmap to Decode mTOR Control System in Cancer. Interdisciplinary Sciences: Computational Life Sciences 2020; 12: 1–11.
[147]. Preau S, Ambler M, Sigurta A, Kleyman A, Dyson A, Hill NE, et al. Protein recycling and limb muscle recovery after critical illness in slow- and fast-twitch limb muscle. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology 2019; 316: R584–R593.
[148]. Chen X, Kondo K, Motoki K, Homma H, Okazawa H. Fasting activates macroautophagy in neurons of Alzheimer’s disease mouse model but is insufficient to degrade amyloid-beta. Scientific Reports 2015; 5: 12115. [PubMed: 26169250]
[149]. Rashidi S, Mansouri R, Ali-Hassanzadeh M, Mojtabadi Z, Shafiei R, Savardashktak A, et al. The host mTOR pathway and parasitic diseases pathogenesis. Parasitology Research 2021; 120: 1151–1166. [PubMed: 33534053]
[150]. Evans T, Kok WL, Cowan K, Hefford M, Anichtchik O. Accumulation of beta-synuclein in cortical neurons is associated with autophagy attenuation in the brains of dementia with Lewy body patients. Brain Research 2018; 1681: 1–13. [PubMed: 29278715]

[151]. Dong W, Wang R, Ma L, Xu B, Zhang J, Zhao Z, et al. Influence of age-related learning and memory capacity of mice: different effects of a high and low caloric diet. Aging Clinical and Experimental Research 2016; 28: 303–311. [PubMed: 26138818]

[152]. Maiese K Forkhead transcription factors: new considerations for Alzheimer’s disease and dementia. Journal of Translational Science 2016; 2: 241–247. [PubMed: 27390624]

[153]. Min J, Huo X, Xiang L, Qin Y, Chai K, Wu B, et al. Protective effect of Dl-3n-butylphthalide on learning and memory impairment induced by chronic intermittent hypoxia-hypercapnia exposure. Scientific Reports 2014; 4: 5555. [PubMed: 24990154]

[154]. Zhang Z, Wu Q, Zheng R, Chen C, Chen Y, Liu Q, et al. Selenomethionine Mitigates Cognitive Decline by Targeting both Tau Hyperphosphorylation and Autophagic Clearance in an Alzheimer’s Disease Mouse Model. The Journal of Neuroscience 2017; 37: 2449–2462. [PubMed: 28137967]

[155]. Chen L, Zhang Y, Li D, Zhang N, Liu R, Han B, et al. Everolimus (RAD001) ameliorates vascular cognitive impairment by regulating microglial function via the mTORC1 signaling pathway. Journal of Neuroimmunology 2016; 299: 164–171. [PubMed: 27725116]

[156]. Chung CL, Lawrence I, Hoffman M, Elgindi D, Nadhan K, Potnis M, et al. Topical rapamycin reduces markers of senescence and aging in human skin: an exploratory, prospective, randomized trial. GeroScience 2019; 41: 861–869. [PubMed: 31761958]

[157]. Park J, Lee C. Temporal changes in mammalian target of rapamycin (mTOR) and phosphorylated-mTOR expressions in the hippocampal CA1 region of rat with vascular dementia. Journal of Veterinary Science 2017; 18: 11–16. [PubMed: 27297423]

[158]. An X, Yao X, Li B, Yang W, Cui R, Zhao G, et al. Role of BDNF-mTORC1 Signaling Pathway in Female Depression. Neural Plasticity 2021; 2021: 6619515. [PubMed: 33347604]

[159]. Martínez de Morentin PB, Martinez-Sanchez N, Roa J, Ferno J, Nogueiras R, Tena-Sempere M, et al. Hypothalamic mTOR: the rookie energy sensor. Current Molecular Medicine 2014; 14: 3–21. [PubMed: 24236459]

[160]. Hwang S, Kim H. The functions of mTOR in ischemic diseases. BMB Reports 2011; 44: 506–511. [PubMed: 21871173]

[161]. Maiese K Erythropoietin and mTOR: a “one-Two Punch” for Aging-Related Disorders Accompanied by Enhanced Life Expectancy. Current Neurovascular Research 2016; 13: 329–340. [PubMed: 27488211]

[162]. Martínez de Morentin PB, Martinez-Sanchez N, Roa J, Ferno J, Nogueiras R, Tena-Sempere M, et al. Hypothalamic mTOR: the rookie energy sensor. Current Molecular Medicine 2014; 14: 3–21. [PubMed: 24236459]

[163]. Maiese K Chapter 1 - Sirtuins in metabolic disease: innovative therapeutic strategies with SIRT1, AMPK, mTOR, and nicotinamide. In Maiese K (Ed.) Sirtuin Biology in Cancer and Metabolic Disease (pp. 3–23). Cambridge: Academic Press, Elsevier. 2021.

[164]. Malla R, Ashby CR, Narayanan NK, Narayanan B, Faridi JS, Tiwari AK. Proline-rich AKT substrate of 40-kDa (PRAS40) in the pathophysiology of cancer. Biochemical and Biophysical Research Communications 2015; 463: 161–166. [PubMed: 26003731]
[169]. Hasbal NB, Turgut D, Gok Oguz E, Ulu S, Gungor O. Effect of Calcineurin Inhibitors and Mammalian Target of Rapamycin Inhibitors on the Course of COVID-19 in Kidney Transplant Recipients. Annals of Transplantation 2021; 26: e929279. [PubMed: 33707409]

[170]. Patocka J, Kuca K, Oleksak P, Nepovimova E, Valis M, Novotny M, et al. Rapamycin: Drug Repurposing in SARS-CoV-2 Infection. Pharmaceuticals 2021; 14: 217. [PubMed: 33807743]

[171]. Pereira G, Leão A, Erustes AG, Morais IBM, Vrechi TAM, Zamarilo LDS, et al. Pharmacological Modulators of Autophagy as a Potential Strategy for the Treatment of COVID-19. International Journal of Molecular Sciences 2021; 22: 4067. [PubMed: 33920748]

[172]. Shi G, Chiramel AI, Majdoul S, Lai KK, Das S, Beare PA, et al. Rapalogs downmodulate intrinsic immunity and promote cell entry of SARS-CoV-2. bioRxiv 2021. (in press)

[173]. Chong ZZ, Shang YC, Wang S, Maiése K. Shedding new light on neurodegenerative diseases through the mammalian target of rapamycin. Progress in Neurobiology 2012; 99: 128–148. [PubMed: 22980037]

[174]. Huang D, Shen S, Cai M, Jin L, Lu J, Xu K, et al. Role of mTOR complex in IGF-1 induced neural differentiation of DPSCs. Journal of Molecular Histology 2019; 50: 273–283. [PubMed: 31049797]

[175]. Jacinto E, Loewith R, Schmidt A, Lin S, Rüegg MA, Hall A, et al. Mammalian TOR complex 2 controls the actin cytoskeleton and is rapamycin insensitive. Nature Cell Biology 2004; 6: 1122–1128. [PubMed: 15467718]

[176]. Joe Y, Chen Y, Park J, Kim HJ, Rah S, Ryu J, et al. Cross-talk between CD38 and TTP is Essential for Resolution of Inflammation during Microbial Sepsis. Cell Reports 2020; 30: 1063–1076.e5. [PubMed: 31995750]

[177]. Pan Y, Song J, Fan B, Wang Y, Che L, Zhang S, et al. MTOR may interact with PARP-1 to regulate visible light-induced parthanatos in photoreceptors. Cell Communication and Signaling 2020; 18: 27. [PubMed: 32066462]

[178]. Wang N, Luo Z, Jin M, Sheng W, Wang H, Long X, et al. Exploration of age-related mitochondrial dysfunction and the antiaging effects of resveratrol in zebrafish retina. Aging 2019; 11: 3117–3137. [PubMed: 31105084]

[179]. Wang R, Kim H, Xiao C, Xu X, Gavrilova O, Deng C. Hepatic Sirt1 deficiency in mice impairs mTorc2/Akt signaling and results in hyperglycemia, oxidative damage, and insulin resistance. The Journal of Clinical Investigation 2011; 121: 4477–4490. [PubMed: 21965330]

[180]. Yin Q, Wang J, Xu X, Xie H. Effect of lycopene on pain facilitation and the SIRT1/mTOR pathway in the dorsal horn of burn injury rats. European Journal of Pharmacology 2020; 889: 173365. [PubMed: 32712090]

[181]. Maiése K. Novel Treatment Strategies for Neurodegenerative Disease with Sirtuins. In Sirtuin Biology in Medicine: Targeting New Avenues of Care in Development, Aging, and Disease Cambridge: Academic Press, Elsevier. 2021.

[182]. Maiése K. MicroRNAs and SIRT1: a Strategy for Stem Cell Renewal and Clinical Development? Journal of Translational Science 2015; 1: 55–57. [PubMed: 26561536]

[183]. Mu N, Lei Y, Wang Y, Wang Y, Duan Q, Ma G, et al. Inhibition of SIRT1/2 upregulates HSPA5 acetylation and induces pro-survival autophagy via ATF4-DDIT4-mTORC1 axis in human lung cancer cells. Apoptosis 2019; 24: 798–811. [PubMed: 31321634]

[184]. Shen C, Dou X, Ma Y, Ma W, Li S, Song Z. Nicotinamide protects hepatocytes against palmitate-induced lipotoxicity via SIRT1-dependent autophagy induction. Nutrition Research 2017; 40: 40–47. [PubMed: 28473059]

[185]. Wang Y, Gao S, Zheng Y, Chen L, Ma M, Shen S, et al. A Novel PDE4D Inhibitor BPN14770 Reverses Scopolamine-Induced Cognitive Deficits via cAMP/SIRT1/Akt/Bcl-2 Pathway. Frontiers in Cell and Developmental Biology 2020; 8: 599389. [PubMed: 33363155]

[186]. Yang J, Suo H, Song J. Protective role of mitoquinone against impaired mitochondrial homeostasis in metabolic syndrome. Critical Reviews in Food Science and Nutrition 2020; 20: 1–19.

[187]. Guo W, Qian L, Zhang J, Zhang W, Morrison A, Hayes P, et al. Sirt1 overexpression in neurons promotes neurite outgrowth and cell survival through inhibition of the mTOR signaling. Journal of Neuroscience Research 2011; 89: 1723–1736. [PubMed: 21826702]
[188]. Ou X, Lee MR, Huang X, Messina-Graham S, Broxmeyer HE. SIRT1 positively regulates autophagy and mitochondria function in embryonic stem cells under oxidative stress. Stem Cells 2014; 32: 1183–1194. [PubMed: 24449278]

[189]. Pal PB, Sonowal H, Shukla K, Srivastava SK, Ramana KV. Aldose reductase regulates hyperglycemia-induced HUVEC death via SIRT1/AMPK-alpha1/mTOR pathway. Journal of Molecular Endocrinology 2019; 63: 11–25. [PubMed: 30986766]

[190]. Zhang H, Yang X, Pang X, Zhao Z, Yu H, Zhou H. Genistein protects against ox-LDL-induced senescence through enhancing SIRT1/LKB1/AIMP-mediated autophagy flux in HUVECs. Molecular and Cellular Biochemistry 2019; 455: 127–134. [PubMed: 30443855]

[191]. Zhang C, Li C, Chen S, Li Z, Ma L, Jia X, et al. Hormetic effect of panaxatriol saponins confers neuroprotection in PC12 cells and zebrafish through PI3K/AKT/mTOR and AMPK/SIRT1/FOX03 pathways. Scientific Reports 2017; 7: 41082. [PubMed: 28112228]

[192]. Caton PW, Kieswich J, Yaqoob MM, Holness MJ, Sugden MC. Metformin opposes impaired AMPK and SIRT1 function and deleterious changes in core clock protein expression in white adipose tissue of genetically-obese db/db mice. Diabetes, Obesity and Metabolism 2011; 13: 1097–1104.

[193]. Sánchez DI, González-Fernández B, Crespo I, San-Miguel B, Álvarez M, González-Gallego J, et al. Melatonin modulates dysregulated circadian clocks in mice with diethylnitrosamine-induced hepatocellular carcinoma. Journal of Pineal Research 2018; 65: e12506. [PubMed: 29770483]

[194]. Sato S, Solanagas G, Peixoto FO, Bee L, Symeonidi A, Schmidt MS, et al. Circadian Reprogramming in the Liver Identifies Metabolic Pathways of Aging. Cell 2017; 170: 664–677.e11. [PubMed: 28802039]

[195]. Charles S, Raj V, Arokiaaraj J, Mala K. Caveolin1/protein arginine methyltransferase1/sirtuin1 axis as a potential target against endothelial dysfunction. Pharmacological Research 2017; 119: 1–11. [PubMed: 28126510]

[196]. Chong ZZ, Shang YC, Wang S, Maiese K. SIRT1: new avenues of discovery for disorders of oxidative stress. Expert Opinion on Therapeutic Targets 2012; 16: 167–178. [PubMed: 22233091]

[197]. Cui L, Guo J, Zhang Q, Yin J, Li J, Zhou W, et al. Erythropoietin activates SIRT1 to protect human cardiomyocytes against doxorubicin-induced mitochondrial dysfunction and toxicity. Toxicology Letters 2017; 275: 28–38. [PubMed: 28456571]

[198]. Geng C, Xu H, Zhang Y, Gao Y, Li M, Liu X, et al. Retinoic acid ameliorates high-fat diet-induced liver steatosis through sirt1. Science China. Life Sciences 2017; 60: 1234–1241. [PubMed: 28667519]

[199]. Maiese K SIRT1 and stem cells: in the forefront with cardiovascular disease, neurodegeneration and cancer. World Journal of Stem Cells 2015; 7: 235–242. [PubMed: 25815111]

[200]. Maiese K Harnessing the Power of SIRT1 and Non-coding RNAs in Vascular Disease. Current Neurovascular Research 2017; 14: 82–88. [PubMed: 27897112]

[201]. Mauilik M, Mitra S, Hunter S, Hunstiger M, Oliver SR, Bult-Ito A, et al. Sir-2.1 mediated attenuation of alpha-synuclein expression by Alaskan bog blueberry polyphenols in a transgenic model of Caenorhabditis elegans. Scientific Reports 2018; 8: 10216. [PubMed: 29976995]

[202]. Sooknual P, Pingaew R, Phopin K, Ruankham W, Prachayasittikul S, Ruchirawat S, et al. Synthesis and neuroprotective effects of novel chalcone-triazole hybrids. Bioorganic Chemistry 2020; 105: 104384. [PubMed: 33130346]

[203]. Maiese K, Chong ZZ, Shang YC, Wang S. Novel directions for diabetes mellitus drug discovery. Expert Opinion on Drug Discovery 2013; 8: 35–48. [PubMed: 23092114]

[204]. Asher G, Gattfield D, Stratmann M, Reinke H, Dibner C, Kreppel F, et al. SIRT1 regulates circadian clock gene expression through per2 deacetylation. Cell 2008; 134: 317–328. [PubMed: 18662546]

[205]. Oblong JE. The evolving role of the NAD+/nicotinamide metabolome in skin homeostasis, cellular bioenergetics, and aging. DNA Repair 2014; 23: 59–63. [PubMed: 24794404]

[206]. Yuan H, Wu G, Zhai X, Lu B, Meng B, Chen J. Melatonin and Rapamycin Attenuate Isoflurane-Induced Cognitive Impairment Through Inhibition of Neuroinflammation by Suppressing the
mTOR Signaling in the Hippocampus of Aged Mice. Frontiers in Aging Neuroscience 2019; 11: 314. [PubMed: 31803045]

[207]. Sharma SK, Ebadi M. Metallothionein attenuates 3-morpholinosydnonimine (SIN-1)-induced oxidative stress in dopaminergic neurons. Antioxidants & Redox Signaling 2003; 5: 251–264. [PubMed: 12880480]

[208]. Vishwas DK, Mukherjee A, Haldar C, Dash D, Nayak MK. Improvement of oxidative stress and immunity by melatonin: an age dependent study in golden hamster. Experimental Gerontology 2013; 48: 168–182. [PubMed: 23220117]

[209]. Zhang G, Deng Y, Xie Q, Ren E, Ma Z, He X, et al. Sirtuins and intervertebral disc degeneration: Roles in inflammation, oxidative stress, and mitochondrial function. Clinica Chimica Acta 2020; 508: 33–42.

[210]. Zhang Y, Zhu X, Wang G, Chen L, Yang H, He F, et al. Melatonin Rescues the Ti Particle-Impaired Osteogenic Potential of Bone Marrow Mesenchymal Stem Cells via the SIRT1/SOD2 Signaling Pathway. Calcified Tissue International 2020; 107: 474–488. [PubMed: 32767062]

[211]. Nakahata Y, Sahar S, Astarita G, Kaluzova M, Sassone-Corsi P. Circadian Control of the NAD+ Salvage Pathway by CLOCK-SIRT1. Science 2009; 324: 654–657. [PubMed: 19286518]

[212]. Hou J, Wang S, Shang YC, Chong ZZ, Maiese K. Erythropoietin employs cell longevity pathways of SIRT1 to foster endothelial vascular integrity during oxidant stress. Current Neurovascular Research 2011; 8: 220–235. [PubMed: 21722091]

[213]. Wang L, Teng R, Di L, Rogers H, Wu H, Kopp JB, et al. PPARalpha and Sirt1 mediate erythropoietin action in increasing metabolic activity and browning of white adipocytes to protect against obesity and metabolic disorders. Diabetes 2013; 62: 4122–4131. [PubMed: 23990359]

[214]. Wu H, Wang H, Zhang W, Wei X, Zhao J, Yan P, et al. RhEPO affects apoptosis in hippocampus of aging rats by upregulating SIRT1. International Journal of Clinical and Experimental Pathology 2015; 8: 6870–6880. [PubMed: 26261574]

[215]. Maiese K New Avenues of Exploration for Erythropoietin. The Journal of the American Medical Association 2005; 293: 90. [PubMed: 15632341]

[216]. Maiese K Regeneration in the nervous system with erythropoietin. Frontiers in Bioscience (Landmark edition) 2016; 21: 561–596.

[217]. Maiese K Erythropoietin and diabetes mellitus. World Journal of Diabetes 2015; 6: 1259–1273. [PubMed: 26516410]

[218]. Maiese K, Chong ZZ, Shang YC. Raves and risks for erythropoietin. Cytokine & Growth Factor Reviews 2008; 19: 145–155. [PubMed: 18299246]

[219]. Ezenwa B, Ezeaka C, Fajolu I, Ogbenna A, Olowoyeye O, Nwaiwu O, et al. Impact of Erythropoietin in the management of Hypoxic Ischaemic Encephalopathy in resource-constrained settings: protocol for a randomized control trial. BMC Neurology 2020; 20: 171. [PubMed: 32366288]

[220]. Govindappa PK, Talukder MAH, Gurjar AA, Hegarty JP, Elfar JC. An effective erythropoietin dose regimen protects against severe nerve injury-induced pathophysiological changes with improved neural gene expression and enhances functional recovery. International Immunopharmacology 2020; 82: 106330. [PubMed: 32143001]

[221]. Jarero-Basulto J, Rivera-Cervantes M, Gasca-Martínez D, García-Sierra F, Gasca-Martínez Y, Beas-Zárate C. Current Evidence on the Protective Effects of Recombinant Human Erythropoietin and Its Molecular Variants against Pathological Hallmarks of Alzheimer’s Disease. Pharmaceuticals 2020; 13: 1–22.

[222]. Rey F, Ottolenghi S, Giallongo T, Balsari A, Martinelli C, Rey R, et al. Mitochondrial Metabolism as Target of the Neuroprotective Role of Erythropoietin in Parkinson’s Disease. Antioxidants 2021; 10: 121. [PubMed: 33467745]

[223]. Vittori DC, Chamorro ME, Hernández YV, Maltaneri RE, Nesse AB. Erythropoietin and derivatives: Potential beneficial effects on the brain. Journal of Neurochemistry 2021. (in press)

[224]. Inkster B, Zai G, Lewis G, Miskowiak KW. GSK3beta: a plausible mechanism of cognitive and hippocampal changes induced by erythropoietin treatment in mood disorders? Translational psychiatry 2018; 8: 216. [PubMed: 30310078]
[225]. Liu W, Varier KM, Sample KM, Zacksenhaus E, Gajendran B, Ben-David Y. Erythropoietin Signaling in the Microenvironment of Tumors and Healthy Tissues. Advances in Experimental Medicine and Biology 2020; 1223: 17–30. [PubMed: 32030683]

[226]. Negri S, Faris P, Rosti V, Antognazza MR, Lodola F, Moccia F. Endothelial TRPV1 as an Emerging Molecular Target to Promote Therapeutic Angiogenesis. Cells 2020; 9: 1341.

[227]. Tang Z, Yang G, Wang X, Chen F, Liao Z, Zhang Z, et al. AKT/GSK-3β/β-catenin signaling pathway participates in erythropoietin-promoted glioma proliferation. Journal of Neuro-Oncology 2020; 149: 231–242. [PubMed: 32909117]

[228]. Caprara C, Grimm C. From oxygen to erythropoietin: relevance of hypoxia for retinal development, health and disease. Progress in Retinal and Eye Research 2012; 31: 89–119. [PubMed: 22108059]

[229]. Maiese K Triple play: promoting neurovascular longevity with nicotinamide, WNT, and erythropoietin in diabetes mellitus. Biomedicine & Pharmacotherapy 2008; 62: 218–232. [PubMed: 18342481]

[230]. Entezari M, Flavarjani ZK, Ramezani A, Nikkhah H, Karimi S, Moghadam HF, et al. Combination of intravitreal bevacizumab and erythropoietin versus intravitreal bevacizumab alone for refractory diabetic macular edema: a randomized double-blind clinical trial. Graefe’s Archive for Clinical and Experimental Ophthalmology 2019; 257: 2375–2380.

[231]. Montesanto A, Bonfigli AR, De Luca M, Crocco P, Garagnani P, Marasco E, et al. Erythropoietin (EPO) haplotype associated with all-cause mortality in a cohort of Italian patients with Type-2 Diabetes. Scientific Reports 2019; 9: 10395. [PubMed: 31316151]

[232]. Chong ZZ, Kang J, Maiese K. Erythropoietin is a novel vascular protectant through activation of Akt1 and mitochondrial modulation of cysteine proteases. Circulation 2002; 106: 2973–2979. [PubMed: 12460881]

[233]. Tani N, Ikeda T, Aoki Y, Shida A, Oritani S, Ishikawa T. Pathophysiological significance of clock genes BMAL1 and per2 as erythropoietin-controlling factors in acute blood hemorrhage. Human Cell 2019; 32: 275–284. [PubMed: 30941700]

[234]. Wang G, Ni Y, Zhou X, Zhang W. The AKT/mTOR pathway mediates neuronal protective effects of erythropoietin in sepsis. Molecular and Cellular Biochemistry 2014; 385: 125–132. [PubMed: 24057122]

[235]. Jang W, Kim HJ, Li H, Jo KD, Lee MK, Yang HO. The Neuroprotective Effect of Erythropoietin on Rotenone-Induced Neurotoxicity in SH-SY5Y Cells through the Induction of Autophagy. Molecular Neurobiology 2015; 53: 3812–3821. [PubMed: 26156288]

[236]. YC, Shang ZZ, Wang S, Maiese K. Prevention of betaamyloid degeneration of microglia by erythropoietin depends on Wnt1, the PI 3-K/mTOR pathway, Bad, and Bcl-xL. Aging 2012; 4: 187–201. [PubMed: 22388478]

[237]. Yu Y, Shiou S, Guo Y, Lu L, Westerhoff M, Sun J, et al. Erythropoietin protects epithelial cells from excessive autophagy and apoptosis in experimental neonatal necrotizing enterocolitis. PLoS ONE 2013; 8: e69620. [PubMed: 23936061]

[238]. Chen Shang Y, Zhong Chong Z, Wang S, Maiese K. WNT1 Inducible Signaling Pathway Protein 1 (WISP1) Targets PRAS40 to Govern beta-Amyloid Apoptotic Injury of Microglia. Current Neurovascular Research 2013; 10: 270–285. [PubMed: 22023617]

[239]. Chong ZZ, Lin S, Kang J, Maiese K. Erythropoietin prevents early and late neuronal demise through modulation of Akt1 and induction of caspase 1, 3, and 8. Journal of Neuroscience Research 2003; 71: 659–669. [PubMed: 12584724]
[243]. Kwon M, Kim M, Kim S, Park K, Yoo S, Oh I, et al. Erythropoietin exerts cell protective effect by activating PI3K/Akt and MAPK pathways in C6 Cells. Neurological Research 2014; 36: 215–223. [PubMed: 24512015]

[244]. Chong ZZ, Shang YC, Wang S, Maiese K. PRAS40 Is an Integral Regulatory Component of Erythropoietin mTOR Signaling and Cytoprotection. PLoS ONE 2012; 7: e45456. [PubMed: 23029019]

[245]. Cheema PS, Nandi D, Nag A. Exploring the therapeutic potential of forkhead box O for outfoxing COVID-19. Open Biology 2021; 11: 210069. [PubMed: 34102081]

[246]. Liu X, Gao C, Qi M, Han Y, Zhou M, Zheng L. Expression of FOXO transcription factors in the brain following traumatic brain injury. Neuroscience Letters 2021; 753: 135882. [PubMed: 33838260]

[247]. Rana T, Behl T, Sehgal A, Mehta V, Singh S, Sharma N, et al. Elucidating the Possible Role of FoxO in Depression. Neurochemical Research 2021. (in press)

[248]. Maiese K, Chong ZZ, Shang YC. OutFOXoing disease and disability: the therapeutic potential of targeting FoxO proteins. Trends in Molecular Medicine 2008; 14: 219–227. [PubMed: 18403263]

[249]. BinMowyna MN, AlFaris NA. Kaempferol suppresses acetaminophen-induced liver damage by upregulation/activation of SIRT1. Pharmaceutical Biology 2021; 59: 146–156. [PubMed: 33562999]

[250]. Rong Y, Ren J, Song W, Xiang R, Ge Y, Lu W, et al. Resveratrol Suppresses Severe Acute Pancreatitis-Induced Microcirculation Disturbance through Targeting SIRT1-FOXO1 Axis. Oxidative Medicine and Cellular Longevity 2021; 2021: 1–8.

[251]. Shati AA, El-Kott AF. Acylated ghrelin protects against Doxorubicin-induced nephropathy by activating SIRT1. Basic and Clinical Pharmacology and Toxicology 2021. (in press)

[252]. Yaman D, Takmaz T, Yüksel N, Dinger SA, Şahin F. Evaluation of silent information regulator T (SIRT) 1 and Forkhead Box O (FOXO) transcription factor 1 and 3a genes in glaucoma. Molecular Biology Reports 2020; 47: 9337–9344. [PubMed: 3300312]

[253]. Chaves I, van der Horst GTJ, Schellevis R, Nijman RM, Koerkamp MG, Holstege FCP, et al. Insulin-FOXO3 signaling modulates circadian rhythms via regulation of clock transcription. Current Biology 2014; 24: 1248–1255. [PubMed: 24856209]

[254]. Maiese K, Chong ZZ, Shang YC, Hou J. FoxO proteins: cunning concepts and considerations for the cardiovascular system. Clinical Science 2009; 116: 191–203. [PubMed: 19118491]

[255]. Sanphui P, Das AK, Biswas SC. FoxO3a requires BAF57, a subunit of chromatin remodeler SWI/SNF complex for induction of PUMA in a model of Parkinson’s disease. Journal of Neurochemistry 2020; 154: e14969.

[256]. Palazuelos J, Klingener M, Aguirre A. TGFbeta signaling regulates the timing of CNS myelination by modulating oligodendrocyte progenitor cell cycle exit through SMAD3/4/FoxO1/Sp1. Journal of Neuroscience 2014; 34: 7917–7930. [PubMed: 24899714]

[257]. Maiese K. Novel Insights for Multiple Sclerosis and Demyelinating Disorders with Apoptosis, Autophagy, FoxO, and mTOR. Current Neurovascular Research 2021; 18: 1–4. [PubMed: 33583379]

[258]. Gökdoğan Edgünlü T, Ünal Y, Karakapı Çelik S, Genç Ö, Emre U, Kutlu G. The effect of FOXO gene family variants and global DNA methylation on RRMS disease. Gene 2020; 726: 144172. [PubMed: 31759981]

[259]. Saleem S, Biswas SC. Tribbles Pseudokinase 3 Induces Both Apoptosis and Autophagy in Amyloid-beta-induced Neuronal Death. Journal of Biological Chemistry 2017; 292: 2571–2585.

[260]. Tabibzadeh S. Signaling pathways and effectors of aging. Frontiers in Bioscience (Landmark edition) 2021; 26: 50–96. [PubMed: 33049665]

[261]. Xiong S, Salazar G, Patrushev N, Alexander RW. FoxO1 Mediates an Autofeedback Loop Regulating SIRT1 Expression. Journal of Biological Chemistry 2011; 286: 5289–5299.

[262]. Lin CL, Huang WN, Li HH, Huang CN, Hsieh S, Lai C, et al. Hydrogen-rich water attenuates amyloid beta-induced cytotoxicity through upregulation of Sirt1-FoxO3a by stimulation of AMP-activated protein kinase in SK-N-MC cells. Chemico-Biological Interactions 2015; 240: 12–21. [PubMed: 26271894]
[263]. Guo P, Wang D, Wang X, Feng H, Tang Y, Sun R, et al. Effect and mechanism of fuzhisan and donepezil on the sirtuin 1 pathway and amyloid precursor protein metabolism in PC12 cells. Molecular Medicine Reports 2016; 13: 3539–3546. [PubMed: 26936536]
Fig. 1. Biological Clock Pathways Are Complex and May Yield Variable Outcomes.
The circadian biological clock gene pathways are intricately related but complex in nature. The pathways of the mechanistic target of rapamycin (mTOR), the silent mating type information regulation 2 homolog 1 (Saccharomyces cerevisiae) (SIRT1), mammalian forkhead transcription factors (FoxOs), the growth factor erythropoietin (EPO), and the wingless Wnt/β-catenin pathway can lead to beneficial outcomes and employ autophagy induction that may provide cellular protection, metabolic homeostasis, and prevent dementia and cognitive loss. Yet, biological clocks and alterations in circadian rhythm, such as during sleep disruption and fragmentation, also have the potential to lead to devastating effects involving tumorigenesis in conjunction with pathways involving Wnt that oversee angiogenesis and stem cell proliferation. Circadian rhythm disruption can result from shift work, exposure to artificial lighting, and from sleep fragmentation. A fine balance in the oversight of circadian biological clock gene pathways is required to foster safe and efficacious clinical outcomes for the treatment of dementia and cognitive loss.
Table 1:

Neurodegeneration and Dementia: Circadian Rhythm Biological Clock Gene Pathways

- Cognitive loss in relation to Alzheimer’s disease is an excellent example of complex disorders that are multi-factorial in origin and may involve several mechanisms as etiologies that include cellular injury from β-amyloid, tau, metabotropic receptors, excitotoxicity, lipid dysfunction, mitochondrial damage, loss of access to bright light, acetylcholine loss, oxidative stress, and metabolic dysfunction with diabetes mellitus.

- Current strategies to treat cognitive loss are limited and do not adequately address disease onset and progression. Innovative work with biological clock genes that oversee circadian rhythm can offer new strategies for the treatment of dementia that employ the pathways of the mechanistic target of rapamycin (mTOR), the silent mating type information regulation 2 homolog 1 (Saccharomyces cerevisiae) (SIRT1), mammalian forkhead transcription factors (FoxOs), the growth factor erythropoietin (EPO), and the wingless Wnt/β-catenin pathway.

- Autophagy in combination with biological clock gene pathways are dependent upon mTOR. Studies suggest that a basal circadian rhythm that modulates autophagy and mTOR pathways involving mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2) may be necessary to prevent cognitive decline and cellular toxicity with amyloid deposition. mTOR also holds an inverse relationship with SIRT1 and these pathways may be necessary to support core circadian components CLOCK and BMAL1 and prevent cellular metabolic dysfunction.

- SIRT1, a histone deacetylase, regulates β-nicotinamide adenine dinucleotide (NAD+) cellular NAD+ pools that fluctuate with circadian rhythmicity and can impact cell function, metabolism, and loss of cognitive function. Oversight with SIRT1 of circadian rhythm pathways may be required for growth factor EPO cellular production and protection.

- FoxOs that can control circadian rhythmicity, such as through the modulation of Clock, can also bind to SIRT1 promoter regions to function through autoregulation mechanisms to regulate SIRT1 activity. SIRT1 and FoxOs can work in unison to block cognitive loss and prevent amyloid toxicity, mitochondrial dysfunction, and oxidative stress injury.

- Wnt proteins are cysteine-rich glycosylated proteins that can affect neuronal development, immunity, tissue fibrosis, angiogenesis, stem cell proliferation, and cancer. Wnt pathways that function in conjunction with circadian clock gene pathways, such as TIMELESS, may promote new angiogenesis and tumorigenesis. Furthermore, disruption of circadian rhythms with sleep fragmentation may increase the risk for developing cancer and other circadian genes that include hClock also may promote the metastasis of colorectal cancer through the enhanced expression of angiogenesis-related genes.