

Review

Cognitive Impairment and Dementia: Gaining Insight through Circadian Clock Gene Pathways

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Abstract: Neurodegenerative disorders affect fifteen percent of the world's population and pose a significant financial burden to all nations. Cognitive impairment is the seventh leading cause of death throughout the globe. Given the enormous challenges to treat cognitive disorders, such as Alzheimer's disease, and the inability to markedly limit disease progression, circadian clock gene pathways offer an exciting strategy to address cognitive loss. Alterations in circadian clock genes can result in age-related motor deficits, affect treatment regimens with neurodegenerative disorders, and lead to the onset and progression of dementia. Interestingly, circadian pathways hold an intricate relationship with autophagy, the mechanistic target of rapamycin (mTOR), the silent mating type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*) (SIRT1), mammalian forkhead transcription factors (FoxOs), and the trophic factor erythropoietin. Autophagy induction is necessary to maintain circadian rhythm homeostasis and limit cortical neurodegenerative disease, but requires a fine balance in biological activity to foster proper circadian clock gene regulation that is intimately dependent upon mTOR, SIRT1, FoxOs, and growth factor expression. Circadian rhythm mechanisms offer innovative prospects for the development of new avenues to comprehend the underlying mechanisms of cognitive loss and forge ahead with new therapeutics for dementia that can offer effective clinical treatments.



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1. The Significant Impact of Cognitive Loss and Neurodegenerative Disease

Non-communicable diseases (NCDs) affect a significant portion of the world's population and it is believed that approximately 70 percent of the annual deaths that occur each year are the result of NCDs [1–3]. NCDs impact a large segment of the population in low- and middle-income countries. At least one-third of this population are under the age of 60 as compared to wealthier nations with only 10 percent of the population affected are under the age of 60 [1]. As an important component of NCDs, neurodegenerative disorders also lead to death and disability in a large proportion of the world's population [4–8]. This is reflected in the role neurodegenerative diseases play in the ten leading causes of death that include cardiac disease, cancer, trauma, respiratory disease, stroke, Alzheimer's disease (AD), diabetes, influenza and pneumonia, kidney disease, and suicide [9]. Neurodegenerative disorders include more than 600 disease entities and lead to disorders in almost one billion individuals throughout the globe [10–15]. This is equivalent to neurodegenerative diseases affecting 15 percent of the world's population and leading to the death of at least 7 million individuals each year [8,16].

It is of interest to note that the age of the global population has been increasing with life expectancy approaching 80 years of age [17] and that the number of individuals over the age of 65 has doubled during the prior 50 years [6,14,18–20]. This includes developed nations, such as the United States (US), where life expectancy was decreasing over a four-year decline, but with a recent reduction in deaths from opioid overdoses, life expectancy

has been increasing again [9]. Yet, as a result of this progressive increase in lifespan and improvements in global healthcare, it is predicted that neurodegenerative diseases will increase in prevalence (Table 1). As an example, dementia is now considered to be the 7th leading cause of death and dementia affects all countries throughout the world at a significant financial burden [2,13,14,21–23]. Almost 5 percent of the world’s elderly population, estimated at 50 million individuals, suffer from dementia. By the year 2030, 82 million people are expected to have dementia, and this will reach 152 million individuals by the year 2050.

Table 1. Highlights—Cognitive Impairment and Dementia: Circadian Clock Gene Pathways.

Neurodegenerative disorders include more than 600 disease entities and currently impact almost one billion individuals throughout the globe, but these numbers are expected to increase with improvements in lifespan and healthcare.
Dementia is the seventh leading cause of death and results in a significant financial burden for all countries throughout the world. Treatment of cognitive disorders is challenging since they are multifactorial and current treatments do not significantly alter disease progression.
Circadian clock gene pathways that involve autophagy, the mechanistic target of rapamycin (mTOR), the silent mating type information regulation 2 homolog 1 (<i>Saccharomyces cerevisiae</i>) (SIRT1), mammalian forkhead transcription factors (FoxOs), and erythropoietin (EPO) offer an exciting prospect to target cognitive loss and dementia.
Alterations in circadian rhythm can lead to reduce lifespan, cognitive impairment, behavior abnormalities, and locomotor deficits. Autophagy pathways that oversee circadian rhythm may limit cognitive loss and protect neurons during toxic insults such as ischemia.
Cognitive decline can be associated with the loss of mTOR activity and altered circadian rhythm. Fluctuations of mTOR activity in conjunction with altered circadian rhythm also may lead to cognitive loss as well as neuronal cell death. In contrast, enhanced mTOR activity with loss of PER2 proteins can alter chemotherapy drug efficacy
SIRT1 control of circadian rhythm and melatonin can affect cellular glucose tolerance, inflammation, and cognitive loss. SIRT1 also can regulate the generation of NAD ⁺ pools that have been linked to aging during circadian rhythmicity. Although an inverse relationship is usually present, SIRT1 can require mTOR and FoxOs for neuroprotection. SIRT1 also relies upon EPO for energy homeostasis and cellular protection that is based upon intact circadian rhythm function.

Cognitive disorders affect more than 5 million individuals in the US alone [24] and almost 60 percent of dementia cases are the result from AD [8,24–29]. Interestingly, it is also believed that dementia is under diagnosed [30,31]. Although AD can affect a significant number of individuals in the world, familial presentations of AD only account for less than 2% of all cases [24]. In these cases, presenilin 1 or 2 gene mutations and amyloid precursor protein (APP) gene mutations can affect 200 families in the world and onset of the disease is before reaching age 55 [15,32,33]. In contrast, sporadic AD occurs at a later age, the $\epsilon 4$ allele of the apolipoprotein E (APOE) gene leads to increased risk, and the disease represents most cases for AD by affecting 10 percent of the population in the world.

In addition to the increasing prevalence of cognitive disorders, significant financial concerns also exist for dementia. Greater than 800 billion United States dollars (USD) is spent to care for individuals with dementia on an annual basis equaling almost 2 percent of the global gross domestic product. It has been predicted that by the year 2030, medical and social services could cost 2 trillion USD annually in the US. At present, more than 5 million individuals are diagnosed with AD and almost 4 million are under treatment at an annual cost of 3.8 billion USD. The annual market size for therapeutic treatments for AD may be underestimated and is expected to currently exceed 11 billion USD. At least 60 million new health and social care workers will be required to fill this need [1,2,34]. These projections do not take into account when to address the need for these healthcare workers in a timely manner. Cognitive loss and dementia may not be recognized until the

late or end stages of the disease. This leaves limited time for effective treatment and may involve fragmented care.

2. Novel Therapeutic Considerations for Cognitive Loss

In general, most neurodegenerative disorders present significant hurdles during diagnosis, treatment, and ability to limit disease progression. Cognitive disorders, such as dementia with AD, raise this bar even further since disorders such as AD are multifactorial in origin. Multiple mechanisms may lead to cognitive impairment and involve cellular injury from β -amyloid ($A\beta$), tau, excitotoxicity, metabotropic receptors, lipid dysfunction, mitochondrial damage, acetylcholine loss, astrocytic cell injury, oxidative stress, heavy metal disease, and cellular metabolic dysfunction with diabetes mellitus (DM) [3,4,8,14,27,35–54]. Present strategies to treat cognitive loss with AD involve therapy with cholinesterase inhibitors that may decrease some symptoms but do not alter disease progression [11,15,52,55]. Additional strategies for dementia can focus on vascular disease [13–15,56,57] and metabolic disease, such as DM [3,4,23,26,52,58]. However, additional risk factors for vascular dementia include hypertension, low education in early life, alcohol consumption, and tobacco use that can limit treatment efficacy [3,22,31,59–61]. In regard to metabolic disorders, early diagnosis and treatment of DM may offer some degree of protection to inhibit disease progression, but tight serum glucose control cannot completely prevent the complications from DM [5,8,16,62–71]. In light of the present challenges to overcome cognitive loss, innovative therapeutic strategies are necessary to develop new treatments for dementia. An exciting prospect to effectively target cognitive loss involves the circadian clock gene pathways that involve autophagy, 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), and the trophic factor erythropoietin (EPO) (Table 1).

3. Circadian Clock Genes, Neurodegeneration, and Cognitive Loss

Circadian rhythm clock genes play a critical role during neurodegenerative disorders and dementia [8,31,72–78] (Table 1). In addition, circadian clock genes affect metabolic disease and cell injury [8,78–87], cell cycle regulation [88–91], cancer [82,83,92–94], energy metabolism and aging [72,76,79,86,95], mitochondrial energy maintenance [78,83,96,97], renal disease [80,92], and viral diseases [74,98–106]. The mammalian circadian clock, located in the suprachiasmatic nucleus (SCN) located above the optic chiasm, receives light input from photosensitive ganglion cells in the retina [8,86,103]. The SCN controls melatonin and cortisol release, the temperature of the body, and can respond to oxidative stress [94,107,108]. The basic helix-loop-helix -PAS (Period-Arnt-Single-minded) transcription factor family oversee *Cryptochrome* (*Cry1* and *Cry2*) and *Period* (*Per1*, *Per2*, and *Per3*) genes [8,80,86,92,109–111]. CLOCK and BMAL1 [90] are part of the family for clock genes with PER:CRY heterodimers able to block transcription controlled by CLOCK:BMAL1 complexes. CLOCK:BMAL1 complexes also can oversee activity of ROR α and NR1D1 (nuclear receptor subfamily 1, group D, member 1), termed retinoic acid-related orphan nuclear receptors REV-ERB α . The REV-ERB α and ROR α receptors link up to retinoic acid-related orphan receptor response elements (ROREs). Once present in the BMAL1 promoter, REV-ERB α and ROR can activate and block rhythmic transcription of BMAL1 to lead to circadian oscillation [76,109].

In relation to neurodegeneration and aging with studies involving *Drosophila melanogaster*, lifespan has been observed to be reduced in three arrhythmic mutants involving ClkAR, cyc0 and tim0. ClkAR mutants had significant faster age-related locomotor deficits. Restoring Clk function was able to rescue *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 rather than directly to the presence of oxidative stress in this case [77]. Furthermore, animal models of Parkinson's disease (PD) with

6-hydroxydopamine (6-OHDA) have shown decreased BMAL1 and ROR α persisted with levodopa treatment, suggesting that long-term levodopa treatment may impair circadian rhythm function and potentially lead to cognitive dysfunction [110]. In regard to cognitive impairment, simulated long duration space flight which changes circadian rhythms leads to cognitive decline and potential neuronal injury [112]. In mouse models of AD, changes in the circadian expression of clock gene RNAs have been observed indicating that they may have a role in dementia [113]. The exposure of light altered clock pathway genes in the SCN to include *Cry1*, *Cry2*, and *Per1*. Furthermore, circadian oscillation of BMAL1 has been seen to be changed in AD patients that may lead to impairment in cognition [72].

4. Circadian Clock Genes, Neurodegeneration, and Sleep Disruption

Impairments in circadian rhythm that lead to sleep fragmentation can lead to further progression in neurodegenerative disorders. Disruptions in daily activity with frequent international travel, shift work, and artificial lighting can lead to circadian rhythm disturbance [81]. Such observations become more evident when one considers potential inter-planetary travel [114]. These incidences of sleep fragmentation can alter nutritional status and affect vitamin D levels and melatonin release that may progress with oxidative stress and mitochondrial injury [6,83,86]. Interestingly, cerebrospinal fluid is facilitated throughout the brain through a glymphatic pathway that involves a peri-vascular network that is required for the removal of metabolic waste during sleep. This system is dependent upon glial cells and loss of sleep can lead to dysfunction of this system and potential progression of neurodegenerative disorders [115]. Sleep deprivation affects circadian homeostasis and can block the removal of A β , tau, α -synuclein that are factors in the pathogenesis of neurodegenerative disorders such as AD and PD. It has been reported that circadian rhythm dysfunction in relation to sleep disturbance can appear in PD patients prior to the onset of motor symptoms [116]. Additionally, loss of a proper sleep-wake cycle with circadian rhythm disruption in elderly individuals has recently been linked to increased risk for COVID-19 infection [74,99,102,104–106]. In individuals with DM, sleep fragmentation can worsen metabolic disease especially in patients with obstructive sleep apnea [117] and promote cell injury through oxidative stress [69,118–120]. Loss of circadian rhythm with sleep fragmentation also can disrupt organs outside of the nervous system such as the heart and lead to cardiovascular dysfunction [121].

5. Circadian Clock Genes and Pathways of Autophagy

Circadian rhythm dysfunction during neuronal injury and cognitive loss has been closely tied to the pathways of autophagy induction [74,83,86,97,119,122,123]. Autophagy has a critical role in multiple neurodegenerative disorders (Table 1). Autophagy can sequester intracellular accumulations that at times may be beneficial during cognitive impairment and AD [14,26,124,125], amyotrophic lateral sclerosis [55,126,127], Huntington's disease (HD) [14,128], traumatic brain injury [129–131], and PD [85,124,129,132–134].

Autophagy as part of the programmed death pathways is linked to oxidative stress [5,16,54,73,135–140]. Autophagy induction recycles cytoplasmic organelles and components for tissue remodeling [14,141] and can remove non-functional organelles [8,73,136,142]. Macroautophagy recycles organelles in cells and sequesters cytoplasmic proteins into autophagosomes. Autophagosomes subsequently combine with lysosomes to become degraded and start a new course for recycling [14]. Microautophagy leads to lysosomal membrane invagination such that components of the cell cytoplasm are sequestered and digested. Chaperone-mediated autophagy depends upon cytosolic chaperones to move components of the cytoplasm across lysosomal membranes.

Interestingly, changes in the environment that includes sleep loss can decrease memory formation in the hippocampus by affecting autophagy proteins [24,122,143–146]. At the cellular level, loss of homeostasis [84,119,147] affects circadian rhythm that impairs cognition [14,23,58,86,140,148]. Activation of autophagy with circadian proteins may be

protective during stroke. It has been observed that cerebral ischemia is worse if the circadian clock protein PER1 is depressed [123]. In animal models of AD, a circadian control of autophagy is necessary to decrease A β accumulation and memory impairment [119,149].

6. Circadian Clock Genes and the Mechanistic Target of Rapamycin

Circadian clock gene pathways through autophagy are reliant upon the mechanistic target of rapamycin (mTOR) [8,86,150–152] (Table 1). mTOR, a 289-kDa serine/threonine protein kinase, is a critical pathway during neurodegenerative disorders and cognitive loss [3,14,50,58,140,153–155]. mTOR is also known as the mammalian target of rapamycin and the FK506-binding protein 12-rapamycin complex-associated protein 1 [14,87,156,157]. mTOR is the primary component of the protein complexes mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2) [158–160]. mTORC1 and mTORC2 are divided into subcomponents [111,140,161–163]. mTORC1 has a number of components. These components are the proline rich Akt substrate 40 kDa (PRAS40), mammalian lethal with Sec13 protein 8, termed mLST8 (mLST8), Raptor, and Deptor (DEP domain-containing mTOR interacting protein) [3,25,164]. PRAS40 blocks binding of p70 ribosomal S6 kinase (p70S6K) and the eukaryotic initiation factor 4E (eIF4E)-binding protein 1 (4EBP1) to Raptor that can affect mTORC1 activity [165,166]. Rapamycin mTORC1 [24] as well inhibits activation of mTORC1 [162,167–170]. mTORC2 has some different components when compared to mTORC1 [171]. These are the protein observed with Rictor-1 (Protor-1), the mammalian stress-activated protein kinase interacting protein (mSIN1), Deptor, mLST8, and Rictor [165,172,173]. mTORC2 can affect migration of cells and changes in the cytoskeleton [174].

Processes that are involved with aging and cognitive loss are dependent upon melatonin, a pineal hormone that controls circadian rhythm [83,94,100], and mTOR in conjunction with autophagy induction [95,175]. Melatonin and the control of the circadian cycle can during aging can be affected infection such as with COVID-19 [99], cellular metabolism [95,108], mitochondrial dysfunction [83], oxidative stress [176,177], and inflammatory mediators [175,178]. Cognitive decline can be associated with the loss of mTOR activity and altered circadian rhythm during prolonged space flight [112]. Cerebral ischemic infarction may be affected by alteration in circadian rhythm genes and fluctuations in mTOR activity [123,150]. In addition, studies suggest that loss of mammalian circadian clock proteins such as period2 (PER2) can lead to enhanced mTOR activity and chemotherapy drug resistance [151].

7. Circadian Clock Genes and the Silent Mating Type Information Regulation 2 Homolog 1 (*Saccharomyces cerevisiae*) (SIRT1)

Circadian clock rhythm pathways are critically dependent upon the silent mating type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*) (SIRT1) [8,86,87,91,96,179] (Table 1). SIRT1 is a histone deacetylase that transfers acetyl groups from ϵ -N-acetyl lysine amino acids to the histones of deoxyribonucleic acid (DNA) to control transcription [14,15,55,86,87,144,180–185]. SIRT1 is involved in neurodegenerative disorders [162,184,186,187] that require the modulation of autophagy [120,188–192].

SIRT1 also is closely associated with the mammalian forkhead transcription proteins [24,55,193–197]. The induction of autophagy relies upon mammalian FOXO proteins of the O class that have an important relationship to neurodegenerative disorders [40,162,187,198,199]. For example, central nervous system myelination involving oligodendrocyte progenitor cells is believed to be controlled through FoxO1 transcription factors [200] that may impact disease such as multiple sclerosis [201]. Other work suggests that progressive pathology of demyelinating disorders may be tied to epigenetic changes with DNA methylation and involve genetic variations of FoxO3a and FoxO1 [202]. FoxO activation during autophagy can be beneficial to cell survival, suggesting that a fine balance in FoxO activity may be required to promote cellular protection and survival. For example, FoxOs through the induction of autophagy can lead to the clearance of toxic intracellular accumulations and promote neuronal survival [203–205].

In regard to SIRT1, SIRT1 activity leads to increased survival through inhibition of FoxO activity [5,14,194–196]. Yet, FoxOs also can bind to the SIRT1 promoter region to alter forkhead transcription [206]. This allows FoxOs to function through autofeedback mechanisms to regulate SIRT1 activity. FoxO proteins, such as those involving FoxO1, have been shown to regulate SIRT1 transcription and increase SIRT1 expression [207]. As a result, it is important to recognize the complex relationship between FoxOs and SIRT1. For example, under some conditions, FoxOs and SIRT1 can function together and synergistically increase the survival of cells. SIRT1 and FoxO3a have been shown to function together to affect cognitive loss and prevent amyloid injury in the brain, mitochondrial dysfunction, and the toxicity of oxidative stress [21,144,208,209].

It is interesting to note that SIRT1 also has an inverse relationship with mTOR [14,189,210–213]. As previously mentioned, SIRT1 also can significantly affect pathways of autophagy [58,69,161,189–191,206,214–216]. SIRT1 activity can result in neurite outgrowth and increased neuronal survival during nutrient limiting conditions with the inhibition of mTOR [217]. SIRT1 also can promote tumor cell growth with autophagy activity that requires mTOR inhibition, suggesting that both SIRT1 and autophagy pathways can be targets to control tumor cell growth [215]. SIRT1 is necessary for protection of mitochondrial function in embryonic stem cells during oxidative stress to promote autophagy and inhibit mTOR activity [218]. During periods of hyperglycemia, SIRT1 can offer protection for vascular cells during inhibition of mTOR activity [219]. Blockade of mTOR with SIRT1 activation may also increase cell survival for photoreceptor cells [211] and limit cell senescence [192]. However, some neurodegenerative pathways require a symbiotic relationship between mTOR and SIRT1. For example, under some conditions that may involve dopaminergic neuronal cell loss a balance in activities of SIRT1, mTOR, and FoxOs are required to achieve neuroprotection [220].

Through a number of pathways involving cellular metabolism, the coenzyme β -nicotinamide adenine dinucleotide (NAD⁺) can play a critical role with circadian rhythm and clock genes that is tied to SIRT1 and mTOR [3,16,74,221,222]. SIRT1 control of circadian rhythm and melatonin may affect cellular glucose tolerance [107], stem cell function [223], and inflammation during obesity [96] and neurodegeneration [178]. In addition, cellular NAD⁺ pools are known to fluctuate with circadian rhythmicity and with aging [74]. If NAD⁺ levels in the cell are diminished, this affects circadian rhythm with cellular levels of nicotinamide to lead to mitochondrial dysfunction and cognitive loss [222]. The circadian rhythm of nicotinamide phosphoribosyl-transferase (NAMPT) is required for NAD⁺ production and is overseen by SIRT1 and the complex of CLOCK:BMAL1. The NAMPT promoter can use SIRT1 to increase production of its own coenzyme [224]. Metformin, an inhibitor of mTOR, can protect SIRT1 activity to maintain proper circadian rhythm of CLOCK and BMAL1 during obesity [221]. Without metformin, the absence of SIRT1 and mTOR block function of CLOCK and BMAL1 during obesity [221]. Yet, other work also suggests that SIRT1 modulates clock genes that involves deacetylation of PER2 [88]. The ability of SIRT1 to oversee several circadian clock gene pathways has suggested that impaired SIRT1 expression can alter circadian rhythm and lead to the loss of cognition and AD [113].

It is of interest to note that SIRT1 regulation of circadian clock genes also may impact cognitive function through trophic factor function, such as erythropoietin (EPO) [159,182,225–227]. The *EPO* gene is located on chromosome 7 and is a single copy in a 5.4 kb region of the genomic DNA [228,229]. This gene encodes for a polypeptide chain protein that has initially 193 amino acids [68,230]. EPO is then processed with the removal of a carboxy-terminal arginine¹⁶⁶ 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 [231–234]. EPO expression is present in the brain, uterus, and liver, but the primary site for the production and secretion of EPO is the kidney peritubular interstitial cells [229,230,235–238]. Expression of EPO is controlled by changes in oxygen tension and not by the concentration of red blood cells [68,239,240]. EPO maintains adipose energy homeostasis in adipocytes to prevent metabolic dysfunction

through the combined activation of peroxisome proliferator-activated receptor- α (PPAR- α) and SIRT1 [226]. EPO also fosters cerebral vascular protection through the subcellular trafficking of SIRT1 to the nucleus and prevents mitochondrial depolarization, cytochrome c release, BCL2 associated agonist of cell death (Bad) activity, and caspase activation [225]. EPO enhances survival of human cardiomyocytes through the activation of SIRT1 during chemotherapy toxicity [182]. EPO also blocks the loss of neuronal cells in the brain through the up-regulation of SIRT1 [227]. In addition, EPO can limit cognitive decline during AD [21,29], oversee metabolic pathways [241,242], and prevent mitochondrial dysfunction [7,182,229,243–245]. EPO has been shown to increase neuronal survival during toxic environments [246] through pathways that involve PRAS40, mTOR and protein kinase B (Akt) [243,247,248]. EPO relies upon mTOR through autophagy and apoptosis to enhance neuronal survival [3,120,249–252], foster microglial function [253], and inhibit activity of caspases in the presence of A β exposure [254]. Yet, without circadian rhythm oversight, the neuroprotective roles of EPO that involve SIRT1 may not exist. Recent work suggests that clock genes, that include *BMAL1* and *PER2*, are necessary for EPO production, such as during toxic events involving hypoxic insults [255].

8. Future Perspectives

Neurodegenerative disorders are a significant component of NCDs and are increasing in prevalence with the rise in lifespan and advances in healthcare that are occurring throughout the world. With these observations, dementia is now considered to be the 7th leading cause of death throughout the globe and poses a significant financial burden to both developed and developing nations leading to more than 800 billion USD spent to care for individuals with dementia on an annual basis. Furthermore, treatment for cognitive disorders, and especially for diseases such as AD, present enormous challenges since such disorders are multifactorial in origin and current strategies do not offer significant advantages to limit disease progression. As a result, innovative strategies are critical to overcome these challenges. Targeting new therapeutic areas with circadian clock gene pathways that involve autophagy, mTOR, SIRT1, FoxOs and EPO offer new possibilities for the treatment of cognitive impairment (Figure 1).

Alterations in circadian clock genes have been shown to lead to age-related motor deficits, cognitive impairment, and potential onset and progression of AD. Chronic treatment regimens, such as during PD, also may eventually impair circadian rhythm function and affect cognitive loss. At the cellular level, a functional circadian rhythm may be vital to oversee autophagy and prevent cognitive decline and the onset of AD. Additional studies suggest that autophagy induction is necessary to maintain a circadian rhythm homeostasis, such as during chronic sleep fragmentation, and to limit cortical disease that can occur during cerebral ischemia. This fine balance in autophagy activation that may be necessary to maintain proper circadian clock gene regulation is intimately linked to mTOR activity. Loss of mTOR activity can lead to altered circadian rhythm and cognitive loss. Furthermore, fluctuations in the activity of mTOR that can impact autophagy induction can result in increased cerebral ischemia and even chemotherapy drug resistance. Interestingly, SIRT1 has an inverse relationship with mTOR under most circumstances to promote cell survival and mitochondrial function. Through these pathways, SIRT1 can control circadian rhythm to affect aging, cellular metabolic pathways, glucose intolerance, cellular inflammation, cognitive loss, and growth factor neuroprotection with EPO. Interestingly, SIRT1 can regulate the generation of NAD⁺ pools that have been linked to aging during circadian rhythmicity. SIRT1 also is tied to FoxOs such that this complex relationship involves FoxO proteins regulating SIRT1 transcription and increasing SIRT1 expression. As a result, FoxOs and SIRT1 can function synergistically at times to affect cognitive loss and prevent A β injury in the brain, mitochondrial dysfunction, and the toxicity of oxidative stress. These observations also correlate with a symbiotic relationship between SIRT1 and mTOR that can occur and involve FoxOs to prevent neurodegenerative cell loss.

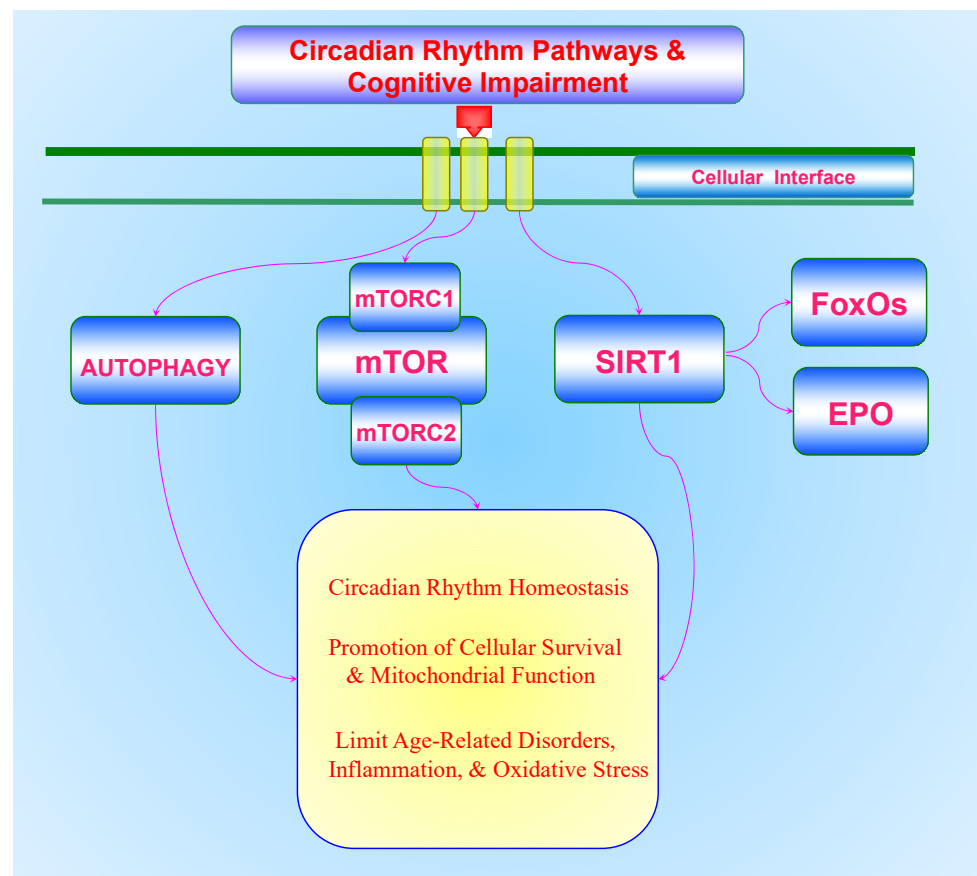


Figure 1. Circadian Rhythm Pathways during Cognitive Impairment. The circadian clock gene pathways provide exciting avenues for the comprehension of the multiple pathways that ultimately can lead to cognitive loss and dementia. These pathways that involve autophagy, the mechanistic target of rapamycin (mTOR), mTOR Complex 1 (mTORC1), mTOR Complex 2 (mTORC2), the silent mating type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*) (SIRT1), mammalian fork-head transcription factors (FoxOs), and erythropoietin (EPO) are complex in nature and require fine biological modulation. Ultimately, circadian rhythm clock genes are critical for the foundation of cognitive health and require maintenance of circadian rhythm homeostasis, prevention of mitochondrial dysfunction that can lead to cellular injury, and preventing the progression of age-related disorders, inflammation, and oxidative stress.

9. Conclusions

The novel circadian clock gene pathways that involve autophagy, mTOR, and (SIRT1) and include FoxOs and EPO offer exciting prospects for the development of new strategies to understand cognitive loss and to overcome challenges that can limit the onset and progression of dementia (Figure 1). Yet, it is clear that these pathways hold intricate relationships with one another that are dependent upon fine biological controls. Further success of the clinical adaptation of these cellular mechanisms will rest upon elucidating the complex nature of these pathways.

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References

1. World Health Organization. Description of the global burden of NCDs, their risk factors and determinants. In *Global Status Report on Noncommunicable Diseases 2010*; World Health Organization: Geneva, Switzerland, 2011; pp. 1–176.
2. World Health Organization. *Global Action Plan on the Public Health Response to Dementia 2017–2025*; World Health Organization: Geneva, Switzerland, 2017; pp. 1–44.
3. Maiese, K. Dysregulation of metabolic flexibility: The impact of mTOR on autophagy in neurodegenerative disease. *Int. Rev. Neurobiol.* **2020**, *155*, 1–35. [[CrossRef](#)]
4. Engin, A.B.; Engin, A. Alzheimer's Disease and Protein Kinases. *Adv. Exp. Med. Biol.* **2021**, *1275*, 285–321. [[CrossRef](#)]
5. Maiese, K. Nicotinamide as a Foundation for Treating Neurodegenerative Disease and Metabolic Disorders. *Curr. Neurovasc. Res.* **2021**. [[CrossRef](#)]
6. Odnokoz, O.; Nakatsuka, K.; Wright, C.; Castellanos, J.; Klichko, V.I.; Kretzschmar, D.; Orr, W.C.; Radyuk, S.N. Mitochondrial Redox Signaling Is Critical to the Normal Functioning of the Neuronal System. *Front. Cell Dev. Biol.* **2021**. [[CrossRef](#)]
7. Rey, F.; Ottolenghi, S.; Giallongo, T.; Balsari, A.; Martinelli, C.; Rey, R.; Allevi, R.; Giulio, A.M.D.; Zuccotti, G.V.; Mazzucchelli, S.; et al. Mitochondrial Metabolism as Target of the Neuroprotective Role of Erythropoietin in Parkinson's Disease. *Antioxidants* **2021**, *10*, 121. [[CrossRef](#)]
8. Maiese, K. Cognitive impairment with diabetes mellitus and metabolic disease: Innovative insights with the mechanistic target of rapamycin and circadian clock gene pathways. *Expert Rev. Clin. Pharmacol.* **2020**, *13*, 23–34. [[CrossRef](#)]
9. National Center for Health Statistics. *National Vital Statistics System*; National Center for Health Statistics: Atlanta, GA, USA, 2019; pp. 1–2.
10. Castro-Portuguez, R.; Sutphin, G.L. Kynurenine pathway, NAD(+) synthesis, and mitochondrial function: Targeting tryptophan metabolism to promote longevity and healthspan. *Exp. Gerontol.* **2020**, *132*, 110841. [[CrossRef](#)] [[PubMed](#)]
11. Cheng, X.; Song, C.; Du, Y.; Gaur, U.; Yang, M. Pharmacological Treatment of Alzheimer's Disease: Insights from *Drosophila melanogaster*. *Int. J. Mol. Sci.* **2020**, *21*, 4621. [[CrossRef](#)] [[PubMed](#)]
12. Lee, E.C.S.; Elhassan, S.A.M.; Lim, G.P.L.; Kok, W.H.; Tan, S.W.; Leong, E.N.; Tan, S.H.; Chan, E.W.L.; Bhattamisra, S.K.; Rajendran, R.; et al. The roles of circular RNAs in human development and diseases. *Biomed. Pharmacother.* **2019**, *111*, 198–208. [[CrossRef](#)] [[PubMed](#)]
13. Wahl, D.; Solon-Biet, S.M.; Cogger, V.C.; Fontana, L.; Simpson, S.J.; Le Couteur, D.G.; Ribeiro, R.V. Aging, lifestyle and dementia. *Neurobiol. Dis.* **2019**, *130*, 104481. [[CrossRef](#)] [[PubMed](#)]
14. Maiese, K. The mechanistic target of rapamycin (mTOR) and the silent mating-type information regulation 2 homolog 1 (SIRT1): Oversight for neurodegenerative disorders. *Biochem. Soc. Trans.* **2018**, *46*, 351–360. [[CrossRef](#)]
15. Maiese, K. Sirtuins: Developing Innovative Treatments for Aged-Related Memory Loss and Alzheimer's Disease. *Curr. Neurovasc. Res.* **2018**, *15*. [[CrossRef](#)]
16. Maiese, K. New Insights for nicotinamide: Metabolic disease, autophagy, and mTOR. *Front. Biosci.* **2020**, *25*, 1925–1973. [[CrossRef](#)]
17. Maiese, K. Cutting through the Complexities of mTOR for the Treatment of Stroke. *Curr. Neurovasc. Res.* **2014**, *11*, 177–186. [[CrossRef](#)]
18. Maiese, K. The bright side of reactive oxygen species: Lifespan extension without cellular demise. *J. Transl. Sci.* **2016**, *2*, 185–187. [[CrossRef](#)]
19. Mladenovic Djordjevic, A.; Loncarevic-Vasiljkovic, N.; Gonos, E.S. Dietary restriction and oxidative stress: Friends or enemies? *Antioxid. Redox Signal.* **2020**. [[CrossRef](#)]
20. Parkhitko, A.A.; Filine, E.; Mohr, S.E.; Moskalev, A.; Perrimon, N. Targeting metabolic pathways for extension of lifespan and healthspan across multiple species. *Ageing Res. Rev.* **2020**, *64*, 101188. [[CrossRef](#)] [[PubMed](#)]
21. Maiese, K. Forkhead Transcription Factors: Formulating a FOXO Target for Cognitive Loss. *Curr. Neurovasc. Res.* **2017**, *14*, 415–420. [[CrossRef](#)] [[PubMed](#)]
22. Maiese, K. Alcohol Use Disorder and Dementia: Critical Mechanisms for Cognitive Loss. *Curr. Neurovasc. Res.* **2021**. [[CrossRef](#)]
23. Su, M.; Naderi, K.; Samson, N.; Youssef, I.; Fulop, L.; Bozso, Z.; Laroche, S.; Delatour, B.; Davis, S. Mechanisms Associated with Type 2 Diabetes as a Risk Factor for Alzheimer-Related Pathology. *Mol. Neurobiol.* **2019**, *56*, 5815–5834. [[CrossRef](#)] [[PubMed](#)]
24. Maiese, K. Taking aim at Alzheimer's disease through the mammalian target of rapamycin. *Ann. Med.* **2014**, *46*, 587–596. [[CrossRef](#)] [[PubMed](#)]
25. Maiese, K.; Chong, Z.Z.; Shang, Y.C.; Wang, S. mTOR: On target for novel therapeutic strategies in the nervous system. *Trends Mol. Med.* **2013**, *19*, 51–60. [[CrossRef](#)] [[PubMed](#)]
26. Hsieh, C.F.; Liu, C.K.; Lee, C.T.; Yu, L.E.; Wang, J.Y. Acute glucose fluctuation impacts microglial activity, leading to inflammatory activation or self-degradation. *Sci. Rep.* **2019**, *9*, 840. [[CrossRef](#)] [[PubMed](#)]
27. Khan, H.; Tundis, R.; Ullah, H.; Aschner, M.; Belwal, T.; Mirzaei, H.; Akkol, E.K. Flavonoids targeting NRF2 in neurodegenerative disorders. *Food Chem. Toxicol.* **2020**, *146*, 111817. [[CrossRef](#)]
28. Kowalska, M.; Piekut, T.; Prendecki, M.; Sodel, A.; Kozubski, W.; Dorszewska, J. Mitochondrial and Nuclear DNA Oxidative Damage in Physiological and Pathological Aging. *DNA Cell Biol.* **2020**, *39*. [[CrossRef](#)]

29. Sun, J.; Martin, J.M.; Vanderpoel, V.; Sumbria, R.K. The Promises and Challenges of Erythropoietin for Treatment of Alzheimer's Disease. *Neuromol. Med.* **2019**, *21*, 12–24. [[CrossRef](#)] [[PubMed](#)]
30. Maiese, K. MicroRNAs for the Treatment of Dementia and Alzheimer's Disease. *Curr. Neurovasc. Res.* **2019**, *16*, 1–2. [[CrossRef](#)]
31. 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 Regen. Res.* **2019**, *14*, 773–774. [[CrossRef](#)] [[PubMed](#)]
32. Agis-Torres, A.; Solhuber, M.; Fernandez, M.; Sanchez-Montero, J.M. Multi-Target-Directed Ligands and other Therapeutic Strategies in the Search of a Real Solution for Alzheimer's Disease. *Curr. Neuropharmacol.* **2014**, *12*, 2–36. [[CrossRef](#)] [[PubMed](#)]
33. Maiese, K. Addressing Alzheimer's Disease and Cognitive Loss through Autophagy. *Curr. Neurovasc. Res.* **2020**, *17*, 339–341. [[CrossRef](#)]
34. World Health Organization. *Dementia: A Public Health Priority*; World Health Organization: Geneva, Switzerland, 2012; pp. 1–4.
35. Caberlotto, L.; Nguyen, T.P.; Lauria, M.; Priami, C.; Rimondini, R.; Maioli, S.; Cedazo-Minguez, A.; Sita, G.; Morroni, F.; Corsi, M.; 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. *Sci. Rep.* **2019**, *9*, 3965. [[CrossRef](#)]
36. Cacabelos, R.; Carril, J.C.; Cacabelos, N.; Kazantsev, A.G.; Vostrov, A.V.; Corzo, L.; Cacabelos, P.; Goldgaber, D. Sirtuins in Alzheimer's Disease: SIRT2-Related GenoPhenotypes and Implications for Pharmacogenetics. *Int. J. Mol. Sci.* **2019**, *20*, 1249. [[CrossRef](#)]
37. Cai, H.; Li, Y.; Niringiyumukiza, J.D.; Su, P.; Xiang, W. Circular RNA involvement in aging: An emerging player with great potential. *Mech. Ageing Dev.* **2019**, *178*, 16–24. [[CrossRef](#)]
38. Chang, R.; Maghribi, A.A.; Vanderpoel, V.; Vasilevko, V.; Cribbs, D.H.; Boado, R.; Pardridge, W.M.; Sumbria, R.K. A Brain Penetrating Bifunctional Erythropoietin-Transferrin Receptor Antibody Fusion Protein for Alzheimer's Disease. *Mol. Pharm.* **2018**. [[CrossRef](#)]
39. Cheng, J.; North, B.J.; Zhang, T.; Dai, X.; Tao, K.; Guo, J.; Wei, W. The emerging roles of protein homeostasis-governing pathways in Alzheimer's disease. *Ageing Cell* **2018**, *17*, e12801. [[CrossRef](#)]
40. Czubowicz, K.; Jesko, H.; Wencel, P.; Lukiw, W.J.; Strosznajder, R.P. The Role of Ceramide and Sphingosine-1-Phosphate in Alzheimer's Disease and Other Neurodegenerative Disorders. *Mol. Neurobiol.* **2019**, *56*, 5436–5455. [[CrossRef](#)] [[PubMed](#)]
41. Duitama, M.; Vargas-López, V.; Casas, Z.; Albarracín, S.L.; Sutachan, J.J.; Torres, Y.P. TRP Channels Role in Pain Associated With Neurodegenerative Diseases. *Front. Neurosci.* **2020**, *14*, 782. [[CrossRef](#)]
42. Gonzalo-Gobernado, R.; Perucho, J.; Vallejo-Muñoz, M.; Casarejos, M.J.; Reimers, D.; Jiménez-Escrig, A.; Gómez, A.; Ulzurrun de Asanza, G.M.; Bazán, E. Liver Growth Factor "LGF" as a Therapeutic Agent for Alzheimer's Disease. *Int. J. Mol. Sci.* **2020**, *21*, 9201. [[CrossRef](#)] [[PubMed](#)]
43. 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. *Front. Mol. Neurosci.* **2020**, *13*, 58. [[CrossRef](#)]
44. Huang, C.; Wen, C.; Yang, M.; Li, A.; Fan, C.; Gan, D.; Li, Q.; Zhao, J.; Zhu, L.; Lu, D. Astaxanthin Improved the Cognitive Deficits in APP/PS1 Transgenic Mice Via Selective Activation of mTOR. *J. Neuroimmune Pharmacol.* **2020**, *1*. [[CrossRef](#)]
45. Li, X.; Li, K.; Chu, F.; Huang, J.; Yang, Z. Graphene oxide enhances β -amyloid clearance by inducing autophagy of microglia and neurons. *Chem. Biol. Interact.* **2020**, *325*, 109126. [[CrossRef](#)] [[PubMed](#)]
46. Maiese, K.; Chong, Z.Z.; Wang, S.; Shang, Y.C. Oxidant Stress and Signal Transduction in the Nervous System with the PI 3-K, Akt, and mTOR Cascade. *Int. J. Mol. Sci.* **2013**, *13*, 13830–13866. [[CrossRef](#)] [[PubMed](#)]
47. Prokopenko, D.; Hecker, J.; Kirchner, R.; Chapman, B.A.; Hoffman, O.; Mullin, K.; Hide, W.; Bertram, L.; Laird, N.; DeMeo, D.L.; et al. Identification of Novel Alzheimer's Disease Loci Using Sex-Specific Family-Based Association Analysis of Whole-Genome Sequence Data. *Sci. Rep.* **2020**, *10*, 5029. [[CrossRef](#)]
48. Sánchez-Melgar, A.; Albasanz, J.L.; Pallàs, M.; Martin, M. Resveratrol Differently Modulates Group I Metabotropic Glutamate Receptors Depending on Age in SAMP8 Mice. *ACS Chem. Neurosci.* **2020**, *11*, 1770–1780. [[CrossRef](#)] [[PubMed](#)]
49. Sedighi, M.; Baluchnejadmojarad, T.; Afshin-Majd, S.; Amiri, M.; Aminzade, M.; Roghani, M. Anti-aging Klotho Protects SH-SY5Y Cells Against Amyloid β 1-42 Neurotoxicity: Involvement of Wnt1/pCREB/Nrf2/HO-1 Signaling. *J. Mol. Neurosci.* **2020**. [[CrossRef](#)] [[PubMed](#)]
50. Wang, H.; Li, Q.; Sun, S.; Chen, S. Neuroprotective Effects of Salidroside in a Mouse Model of Alzheimer's Disease. *Cell Mol. Neurobiol.* **2020**, *40*, 1133–1142. [[CrossRef](#)] [[PubMed](#)]
51. Wang, Y.; Lin, Y.; Wang, L.; Zhan, H.; Luo, X.; Zeng, Y.; Wu, W.; Zhang, X.; Wang, F. TREM2 ameliorates neuroinflammatory response and cognitive impairment via PI3K/AKT/FoxO3a signaling pathway in Alzheimer's disease mice. *Ageing* **2020**, *12*, 20862. [[CrossRef](#)] [[PubMed](#)]
52. Hu, Z.; Jiao, R.; Wang, P.; Zhu, Y.; Zhao, J.; De Jager, P.; Bennett, D.A.; Jin, L.; Xiong, M. Shared Causal Paths underlying Alzheimer's dementia and Type 2 Diabetes. *Sci. Rep.* **2020**, *10*, 4107. [[CrossRef](#)] [[PubMed](#)]
53. Zhang, W.; Bai, S.; Yang, J.; Zhang, Y.; Liu, Y.; Nie, J.; Meng, D.; Shi, R.; Yao, Z.; Wang, M.; et al. FoxO1 overexpression reduces A β production and tau phosphorylation in vitro. *Neurosci. Lett.* **2020**, *738*, 135322. [[CrossRef](#)]
54. Fang, Y.; Lu, L.; Liang, Y.; Peng, D.; Aschner, M.; Jiang, Y. Signal transduction associated with lead-induced neurological disorders: A review. *Food Chem. Toxicol.* **2021**, *150*, 112063. [[CrossRef](#)] [[PubMed](#)]
55. Maiese, K. FoxO Proteins in the Nervous System. *Anal. Cell Pathol.* **2015**, *2015*, 569392. [[CrossRef](#)] [[PubMed](#)]

56. Maiese, K.; Chong, Z.Z.; Hou, J.; Shang, Y.C. New strategies for Alzheimer's disease and cognitive impairment. *Oxidative Med. Cell. Longev.* **2009**, *2*, 279–289. [[CrossRef](#)]
57. Chen, F.; Liu, Z.; Peng, W.; Gao, Z.; Ouyang, H.; Yan, T.; Ding, S.; Cai, Z.; Zhao, B.; Mao, L.; 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. *Exp. Ther. Med.* **2018**, *16*, 2651–2658. [[CrossRef](#)]
58. Maiese, K. Novel nervous and multi-system regenerative therapeutic strategies for diabetes mellitus with mTOR. *Neural Regen. Res.* **2016**, *11*, 372–385. [[CrossRef](#)]
59. Bahorik, A.; Bobrow, K.; Hoang, T.; Yaffe, K. Increased risk of dementia in older female US veterans with alcohol use disorder. *Addiction* **2021**. [[CrossRef](#)] [[PubMed](#)]
60. Ong, W.Y.; Wu, Y.J.; Farooqui, T.; Farooqui, A.A. Qi Fu Yin—a Ming Dynasty Prescription for the Treatment of Dementia. *Mol. Neurobiol.* **2018**, *55*, 7389–7400. [[CrossRef](#)] [[PubMed](#)]
61. Song, D.Y.; Wang, X.W.; Wang, S.; Ge, S.Q.; Ding, G.Y.; Chen, X.Y.; Chen, Y.R.; Liu, H.M.; Xie, X.M.; Xing, W.J.; et al. Jidong cognitive impairment cohort study: Objectives, design, and baseline screening. *Neural Regen. Res.* **2020**, *15*, 1111–1119. [[CrossRef](#)] [[PubMed](#)]
62. Coca, S.G.; Ismail-Beigi, F.; Haq, N.; Krumholz, H.M.; Parikh, C.R. Role of intensive glucose control in development of renal end points in type 2 diabetes mellitus: Systematic review and meta-analysis intensive glucose control in type 2 diabetes. *Arch. Intern. Med.* **2012**, *172*, 761–769. [[CrossRef](#)] [[PubMed](#)]
63. Barchetta, I.; Cimini, F.A.; Ciccarelli, G.; Baroni, M.G.; Cavallo, M.G. Sick fat: The good and the bad of old and new circulating markers of adipose tissue inflammation. *J. Endocrinol. Investig.* **2019**, *42*, 1257–1272. [[CrossRef](#)] [[PubMed](#)]
64. Fan, X.; Zhao, Z.; Wang, D.; Xiao, J. Glycogen synthase kinase-3 as a key regulator of cognitive function. *Acta Biochim. Biophys. Sin.* **2020**, *52*, 219–230. [[CrossRef](#)]
65. Fernandez-Ruiz, R.; García-Alamán, A.; Esteban, Y.; Mir-Coll, J.; Serra-Navarro, B.; Fontcuberta-PiSunyer, M.; Broca, C.; Armanet, M.; Wojtusciszyn, A.; Kram, V.; et al. Wisp1 is a circulating factor that stimulates proliferation of adult mouse and human beta cells. *Nat. Commun.* **2020**, *11*, 5982. [[CrossRef](#)]
66. Januszewski, A.S.; Watson, C.J.; O'Neill, V.; McDonald, K.; Ledwidge, M.; Robson, T.; Jenkins, A.J.; Keech, A.C.; McClements, L. FKBPL is associated with metabolic parameters and is a novel determinant of cardiovascular disease. *Sci. Rep.* **2020**, *10*, 21655. [[CrossRef](#)]
67. Liu, L.; Hu, J.; Yang, L.; Wang, N.; Liu, Y.; Wei, X.; Gao, M.; Wang, Y.; Ma, Y.; Wen, D. Association of WISP1/CCN4 with Risk of Overweight and Gestational Diabetes Mellitus in Chinese Pregnant Women. *Dis. Markers* **2020**, *2020*, 4934206. [[CrossRef](#)]
68. Maiese, K. Novel applications of trophic factors, Wnt and WISP for neuronal repair and regeneration in metabolic disease. *Neural Regen. Res.* **2015**, *10*, 518–528. [[CrossRef](#)] [[PubMed](#)]
69. Maiese, K. New Insights for Oxidative Stress and Diabetes Mellitus. *Oxidative Med. Cell. Longev.* **2015**, *2015*. [[CrossRef](#)]
70. Saenwongsa, W.; Nithichanon, A.; Chittaganpitch, M.; Buayai, K.; Kewcharoenwong, C.; Thumrongwilainet, B.; Butta, P.; Palaga, T.; Takahashi, Y.; Ato, M.; et al. Metformin-induced suppression of IFN-alpha via mTORC1 signalling following seasonal vaccination is associated with impaired antibody responses in type 2 diabetes. *Sci. Rep.* **2020**, *10*, 3229. [[CrossRef](#)] [[PubMed](#)]
71. Yamashima, T.; Ota, T.; Mizukoshi, E.; Nakamura, H.; Yamamoto, Y.; Kikuchi, M.; Yamashita, T.; Kaneko, S. Intake of ω -6 Polyunsaturated Fatty Acid-Rich Vegetable Oils and Risk of Lifestyle Diseases. *Adv. Nutr.* **2020**, *11*, 1489–1509. [[CrossRef](#)]
72. Cronin, P.; McCarthy, M.J.; Lim, A.S.P.; Salmon, D.P.; Galasko, D.; Masliah, E.; De Jager, P.L.; Bennett, D.A.; Desplats, P. Circadian alterations during early stages of Alzheimer's disease are associated with aberrant cycles of DNA methylation in BMAL1. *Alzheimer's Dement. J. Alzheimer's Assoc.* **2017**, *13*, 689–700. [[CrossRef](#)] [[PubMed](#)]
73. Klionsky, D.J.; Abdel-Aziz, A.K.; Abdelfatah, S.; Abdellatif, M.; Abdoli, A.; Abel, S.; Abeliovich, H.; Abildgaard, M.H.; Abudu, Y.P.; Acevedo-Arozena, A.; et al. Guidelines for the use and interpretation of assays for monitoring autophagy (4th edition). *Autophagy* **2021**, *17*, 1–382. [[CrossRef](#)]
74. Maiese, K. Nicotinamide: Oversight of Metabolic Dysfunction through SIRT1, mTOR, and Clock Genes. *Curr. Neurovasc. Res.* **2020**, *17*. [[CrossRef](#)]
75. Hardeland, R. Neuroprotection by radical avoidance: Search for suitable agents. *Molecules* **2009**, *14*, 5054–5102. [[CrossRef](#)] [[PubMed](#)]
76. Hood, S.; Amir, S. Neurodegeneration and the Circadian Clock. *Front. Aging Neurosci.* **2017**, *9*, 170. [[CrossRef](#)]
77. Vaccaro, A.; Issa, A.R.; 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 Genet.* **2017**, *13*, e1006507. [[CrossRef](#)]
78. Zhang, H.; Liang, J.; Chen, N. Do not neglect the role of circadian rhythm in muscle atrophy. *Ageing Res. Rev.* **2020**, *63*, 101155. [[CrossRef](#)] [[PubMed](#)]
79. De Nobrega, A.K.; Luz, K.V.; Lyons, L.C. Resetting the Aging Clock: Implications for Managing Age-Related Diseases. *Adv. Exp. Med. Biol.* **2020**, *1260*, 193–265. [[CrossRef](#)]
80. Egstrand, S.; Olgaard, K.; Lewin, E. Circadian rhythms of mineral metabolism in chronic kidney disease-mineral bone disorder. *Curr. Opin. Nephrol. Hypertens* **2020**, *29*, 367–377. [[CrossRef](#)]
81. Finger, A.M.; Kramer, A. Mammalian circadian systems: Organization and modern life challenges. *Acta Physiol.* **2020**, e13548. [[CrossRef](#)] [[PubMed](#)]

82. Ma, D.; Hou, L.; Xia, H.; Li, H.; Fan, H.; Jia, X.; Niu, Z. PER2 inhibits proliferation and stemness of glioma stem cells via the Wnt/ β -catenin signaling pathway. *Oncol. Rep.* **2020**, *44*, 533–542. [[CrossRef](#)]
83. Mocayar Marón, F.J.; Ferder, L.; Reiter, R.J.; Manucha, W. Daily and seasonal mitochondrial protection: Unraveling common possible mechanisms involving vitamin D and melatonin. *J. Steroid Biochem. Mol. Biol.* **2020**, *199*, 105595. [[CrossRef](#)]
84. Qi, X.; Mitter, S.K.; Yan, Y.; Busik, J.V.; Grant, M.B.; Boulton, M.E. Diurnal Rhythmicity of Autophagy Is Impaired in the Diabetic Retina. *Cells* **2020**, *9*, 905. [[CrossRef](#)]
85. Tatullo, M.; Marrelli, B.; Zullo, M.J.; Codispoti, B.; Paduano, F.; Benincasa, C.; Fortunato, F.; Scacco, S.; Zavan, B.; Cocco, T. Exosomes from Human Periapical Cyst-MSCs: Theranostic Application in Parkinson's Disease. *Int. J. Med. Sci.* **2020**, *17*, 657–663. [[CrossRef](#)]
86. Maiese, K. Moving to the Rhythm with Clock (Circadian) Genes, Autophagy, mTOR, and SIRT1 in Degenerative Disease and Cancer. *Curr. Neurovasc. Res.* **2017**, *14*, 299–304. [[CrossRef](#)]
87. Maiese, K. Novel Treatment Strategies for the Nervous System: Circadian Clock Genes, Non-coding RNAs, and Forkhead Transcription Factors. *Curr. Neurovasc. Res.* **2018**, *15*, 81–91. [[CrossRef](#)]
88. Asher, G.; Gatfield, D.; Stratmann, M.; Reinke, H.; Dibner, C.; Kreppel, F.; Mostoslavsky, R.; Alt, F.W.; Schibler, U. SIRT1 regulates circadian clock gene expression through PER2 deacetylation. *Cell* **2008**, *134*, 317–328. [[CrossRef](#)] [[PubMed](#)]
89. Bellet, M.M.; Masri, S.; Astarita, G.; Sassone-Corsi, P.; Della Fazia, M.A.; Servillo, G. Histone Deacetylase SIRT1 Controls Proliferation, Circadian Rhythm, and Lipid Metabolism during Liver Regeneration in Mice. *J. Biol. Chem.* **2016**, *291*, 23318–23329. [[CrossRef](#)] [[PubMed](#)]
90. 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 Biochem. Funct.* **2013**, *31*, 166–172. [[CrossRef](#)]
91. Sanchez, D.I.; Gonzalez-Fernandez, B.; Crespo, I.; San-Miguel, B.; Alvarez, M.; Gonzalez-Gallego, J.; Tunon, M.J. Melatonin modulates dysregulated circadian clocks in mice with diethylnitrosamine-induced hepatocellular carcinoma. *J. Pineal Res.* **2018**, *65*, e12506. [[CrossRef](#)]
92. Angelousi, A.; Kassi, E.; Ansari-Nasiri, N.; Randevara, H.; Kaltsas, G.; Chrousos, G. Clock genes and cancer development in particular in endocrine tissues. *Endocr. Relat. Cancer* **2019**, *26*, R305–R317. [[CrossRef](#)]
93. 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. *Int. J. Clin. Exp. Pathol.* **2020**, *13*, 2297–2304. [[PubMed](#)]
94. Bonmati-Carrion, M.A.; Tomas-Loba, A. Melatonin and Cancer: A Polyhedral Network Where the Source Matters. *Antioxidants* **2021**, *10*, 210. [[CrossRef](#)]
95. Jenwitheesuk, A.; Nopparat, C.; Mukda, S.; Wongchitrat, P.; Govitrapong, P. Melatonin regulates aging and neurodegeneration through energy metabolism, epigenetics, autophagy and circadian rhythm pathways. *Int. J. Mol. Sci.* **2014**, *15*, 16848–16884. [[CrossRef](#)] [[PubMed](#)]
96. 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. *J. Pineal Res.* **2018**, *64*, 12455. [[CrossRef](#)] [[PubMed](#)]
97. Rossetti, M.L.; Esser, K.A.; Lee, C.; Tomko, R.J., Jr.; Eroshkin, A.M.; Gordon, B.S. Disruptions to the Limb Muscle Core Molecular Clock Coincide with Changes in Mitochondrial Quality Control following Androgen Depletion. *Am. J. Physiol. Endocrinol. Metab.* **2019**, *317*, E631–E645. [[CrossRef](#)]
98. Borrmann, H.; Davies, R.; Dickinson, M.; Pedroza-Pacheco, I.; Schilling, M.; Vaughan-Jackson, A.; Magri, A.; James, W.; Balfe, P.; Borrow, P.; et al. Pharmacological activation of the circadian component REV-ERB inhibits HIV-1 replication. *Sci. Rep.* **2020**, *10*, 13271. [[CrossRef](#)] [[PubMed](#)]
99. Cardinali, D.P.; Brown, G.M.; Reiter, R.J.; Pandi-Perumal, S.R. Elderly as a High-risk Group during COVID-19 Pandemic: Effect of Circadian Misalignment, Sleep Dysregulation and Melatonin Administration. *Sleep Vigil.* **2020**, *4*, 81–87. [[CrossRef](#)] [[PubMed](#)]
100. Crespo, I.; Fernández-Palanca, P.; San-Miguel, B.; Álvarez, M.; González-Gallego, J.; Tuñón, M.J. Melatonin modulates mitophagy, innate immunity and circadian clocks in a model of viral-induced fulminant hepatic failure. *J. Cell Mol. Med.* **2020**, *24*, 7625–7636. [[CrossRef](#)]
101. Lim, R.K.; Wambier, C.G.; Goren, A. Are night shift workers at an increased risk for COVID-19? *Med. Hypotheses* **2020**, *144*, 110147. [[CrossRef](#)]
102. Maiese, K. Circadian Clock Genes: Targeting Innate Immunity for Antiviral Strategies Against COVID-19. *Curr. Neurovasc. Res.* **2020**. [[CrossRef](#)]
103. 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. [[CrossRef](#)]
104. Morin, C.M.; Carrier, J.; Bastien, C.; Godbout, R. Sleep and circadian rhythm in response to the COVID-19 pandemic. *Can. J. Public Health* **2020**, *111*, 654–657. [[CrossRef](#)]
105. Tamimi, F.; Abusamak, M.; Akkanti, B.; Chen, Z.; Yoo, S.H.; Karmouty-Quintana, H. The case for chronotherapy in COVID-19-induced acute respiratory distress syndrome. *Br. J. Pharmacol.* **2020**, *177*, 4845–4850. [[CrossRef](#)]
106. Maiese, K. The Mechanistic Target of Rapamycin (mTOR): Novel Considerations as an Antiviral Treatment. *Curr. Neurovasc. Res.* **2020**, *17*, 332–337. [[CrossRef](#)]
107. Hardeland, R. Melatonin and the pathologies of weakened or dysregulated circadian oscillators. *J. Pineal Res.* **2017**, *62*, 12377. [[CrossRef](#)] [[PubMed](#)]

108. Jenwitheesuk, A.; Park, S.; Wongchitrat, P.; Tocharus, J.; Mukda, S.; Shimokawa, I.; Govitrapong, P. Comparing the Effects of Melatonin with Caloric Restriction in the Hippocampus of Aging Mice: Involvement of Sirtuin1 and the FOXOs Pathway. *Neurochem. Res.* **2017**. [[CrossRef](#)] [[PubMed](#)]
109. Bunney, B.G.; Li, J.Z.; Walsh, D.M.; Stein, R.; Vawter, M.P.; Cartagena, P.; Barchas, J.D.; Schatzberg, A.F.; Myers, R.M.; Watson, S.J.; et al. Circadian dysregulation of clock genes: Clues to rapid treatments in major depressive disorder. *Mol. Psychiatry* **2015**, *20*, 48–55. [[CrossRef](#)] [[PubMed](#)]
110. Li, S.Y.; Wang, Y.L.; Liu, W.W.; Lyu, D.J.; Wang, F.; Mao, C.J.; Yang, Y.P.; Hu, L.F.; Liu, C.F. Long-term Levodopa Treatment Accelerates the Circadian Rhythm Dysfunction in a 6-hydroxydopamine Rat Model of Parkinson's Disease. *Chin. Med. J.* **2017**, *130*, 1085–1092. [[CrossRef](#)]
111. Yu, M.; Zhang, H.; Wang, B.; Zhang, Y.; Zheng, X.; Shao, B.; Zhuge, Q.; Jin, K. Key Signaling Pathways in Aging and Potential Interventions for Healthy Aging. *Cells* **2021**, *10*, 660. [[CrossRef](#)] [[PubMed](#)]
112. Wu, X.; Li, D.; Liu, J.; Diao, L.; Ling, S.; Li, Y.; Gao, J.; Fan, Q.; Sun, W.; Li, Q.; et al. Dammarane Sapogenins Ameliorates Neurocognitive Functional Impairment Induced by Simulated Long-Duration Spaceflight. *Front. Pharmacol.* **2017**, *8*, 315. [[CrossRef](#)]
113. Bellanti, F.; Iannelli, G.; Blonda, M.; Tamborra, R.; Villani, R.; Romano, A.; Calcagnini, S.; Mazzoccoli, G.; Vinciguerra, M.; Gaetani, S.; et al. Alterations of Clock Gene RNA Expression in Brain Regions of a Triple Transgenic Model of Alzheimer's Disease. *J. Alzheimers Dis.* **2017**, *59*, 615–631. [[CrossRef](#)]
114. Frantzydiz, C.A.; Kontana, E.; Karkala, A.; Nigdelis, V.; Karagianni, M.; Nday, C.M.; Ganapathy, K.; Kourtidou-Papadeli, C. Current trends and future perspectives of space neuroscience towards preparation for interplanetary missions. *Neurol. India* **2019**, *67*, S182–S187. [[CrossRef](#)]
115. Benveniste, H.; Lee, H.; Volkow, N.D. The Glymphatic Pathway: Waste Removal from the CNS via Cerebrospinal Fluid Transport. *Neuroscientist* **2017**, *23*, 454–465. [[CrossRef](#)] [[PubMed](#)]
116. Liu, Y.; Niu, L.; Liu, X.; Cheng, C.; Le, W. Recent Progress in Non-motor Features of Parkinson's Disease with a Focus on Circadian Rhythm Dysregulation. *Neurosci. Bull.* **2021**. [[CrossRef](#)] [[PubMed](#)]
117. Elnour, M.A.A.; Saleh, A.A.; Kalantan, M.M.; Mirghani, H.O. The relationship between coffee intake, obstructive sleep apnea risk, and type 2 diabetes glycemic control, in Tabuk City, The Kingdom of Saudi Arabia: A case-control study. *BMC Res. Notes* **2019**, *12*, 798. [[CrossRef](#)] [[PubMed](#)]
118. Papachristoforou, E.; Lambadiari, V.; Maratou, E.; Makrilakis, K. Association of Glycemic Indices (Hyperglycemia, Glucose Variability, and Hypoglycemia) with Oxidative Stress and Diabetic Complications. *J. Diabetes Res.* **2020**, *2020*, 7489795. [[CrossRef](#)] [[PubMed](#)]
119. Wang, X.; Xu, Z.; Cai, Y.; Zeng, S.; Peng, B.; Ren, X.; Yan, Y.; Gong, Z. Rheostatic Balance of Circadian Rhythm and Autophagy in Metabolism and Disease. *Front. Cell Dev. Biol.* **2020**, *24*. [[CrossRef](#)]
120. Maiese, K.; Chong, Z.Z.; Shang, Y.C.; Wang, S. Novel directions for diabetes mellitus drug discovery. *Expert Opin. Drug Discov.* **2013**, *8*, 35–48. [[CrossRef](#)]
121. Liu, H.; Chen, A. Roles of sleep deprivation in cardiovascular dysfunctions. *Life Sci.* **2019**, *219*, 231–237. [[CrossRef](#)]
122. He, Y.; Cornelissen-Guillaume, G.G.; He, J.; Kastin, A.J.; Harrison, L.M.; Pan, W. Circadian rhythm of autophagy proteins in hippocampus is blunted by sleep fragmentation. *Chronobiol. Int.* **2016**, *33*, 553–560. [[CrossRef](#)]
123. Rami, A.; Rawashdeh, O. The hippocampal autophagic machinery is depressed in the absence of the circadian clock protein PER1 that may lead to vulnerability during cerebral ischemia. *Curr. Neurovasc. Res.* **2017**, *14*, 207–214. [[CrossRef](#)]
124. Zhang, Y.; Wu, Q.; Zhang, L.; Wang, Q.; Yang, Z.; Liu, J.; Feng, L. 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. *Pharmacol. Res.* **2019**, *150*, 104538. [[CrossRef](#)]
125. Zhou, T.; Zhuang, J.; Wang, Z.; Zhou, Y.; Li, W.; Wang, Z.; Zhu, Z. Glaucoalyxin 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. [[CrossRef](#)]
126. Francois, A.; Terro, F.; Quellard, N.; Fernandez, B.; Chassaing, D.; Janet, T.; Rioux-Bilan, A.; Paccalin, M.; Page, G. Impairment of autophagy in the central nervous system during lipopolysaccharide-induced inflammatory stress in mice. *Mol. Brain* **2014**, *7*, 56. [[CrossRef](#)]
127. Sullivan, P.M.; Zhou, X.; Robins, A.M.; Paushter, D.H.; Kim, D.; Smolka, M.B.; Hu, F. The ALS/FTLD associated protein C9orf72 associates with SMCR8 and WDR41 to regulate the autophagy-lysosome pathway. *Acta Neuropathol. Commun.* **2016**, *4*, 51. [[CrossRef](#)] [[PubMed](#)]
128. Lee, J.H.; Tecedor, L.; Chen, Y.H.; Monteys, A.M.; Sowada, M.J.; Thompson, L.M.; Davidson, B.L. Reinstating aberrant mTORC1 activity in Huntington's disease mice improves disease phenotypes. *Neuron* **2015**, *85*, 303–315. [[CrossRef](#)] [[PubMed](#)]
129. Maiese, K. Targeting molecules to medicine with mTOR, autophagy and neurodegenerative disorders. *Br. J. Clin. Pharmacol.* **2016**, *82*, 1245–1266. [[CrossRef](#)] [[PubMed](#)]
130. 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 Int.* **2017**, *2017*, 4782820. [[CrossRef](#)]
131. Zhang, P.; Ye, Y.; Qian, Y.; Yin, B.; Zhao, J.; Zhu, S.; Zhang, L.; Yan, M. The effect of pyrroloquinoline quinone on apoptosis and autophagy in traumatic brain injury. *CNS Neurol. Disord. Drug Targets* **2017**, *16*, 724–736. [[CrossRef](#)] [[PubMed](#)]

132. Corti, O.; Blomgren, K.; Poletti, A.; Beart, P.M. Autophagy in neurodegeneration: New insights underpinning therapy for neurological diseases. *J. Neurochem.* **2020**, *154*, e15002. [[CrossRef](#)] [[PubMed](#)]
133. Fields, C.R.; Bengoa-Vergniory, N.; Wade-Martins, R. Targeting Alpha-Synuclein as a Therapy for Parkinson's Disease. *Front. Mol. Neurosci.* **2019**, *12*, 299. [[CrossRef](#)] [[PubMed](#)]
134. Zhou, Z.D.; Selvaratnam, T.; Lee, J.C.T.; Chao, Y.X.; Tan, E.K. Molecular targets for modulating the protein translation vital to proteostasis and neuron degeneration in Parkinson's disease. *Transl. Neurodegener.* **2019**, *8*, 6. [[CrossRef](#)] [[PubMed](#)]
135. Jayaraj, R.L.; Beiram, R.; Azimullah, S.; Mf, N.M.; Ojha, S.K.; Adem, A.; Jalal, F.Y. Valeric Acid Protects Dopaminergic Neurons by Suppressing Oxidative Stress, Neuroinflammation and Modulating Autophagy Pathways. *Int. J. Mol. Sci.* **2020**, *21*, 7670. [[CrossRef](#)]
136. Maiese, K.; Chong, Z.Z.; Shang, Y.C.; Wang, S. Targeting disease through novel pathways of apoptosis and autophagy. *Expert Opin. Ther. Targets* **2012**, *16*, 1203–1214. [[CrossRef](#)]
137. 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. [[CrossRef](#)]
138. Xie, T.; Ye, W.; Liu, J.; Zhou, L.; Song, Y. The Emerging Key Role of Klotho in the Hypothalamus-Pituitary-Ovarian Axis. *Reprod. Sci.* **2021**, *28*, 322–331. [[CrossRef](#)] [[PubMed](#)]
139. Zhou, Q.; Tang, S.; Zhang, X.; Chen, L. Targeting PRAS40: A novel therapeutic strategy for human diseases. *J. Drug Target.* **2021**, 1–44. [[CrossRef](#)] [[PubMed](#)]
140. Perluigi, M.; Di Domenico, F.; Barone, E.; Butterfield, D.A. mTOR in Alzheimer disease and its earlier stages: Links to oxidative damage in the progression of this dementing disorder. *Free Radic. Biol. Med.* **2021**, *169*, 382–396. [[CrossRef](#)] [[PubMed](#)]
141. Dorvash, M.; Farahmandnia, M.; Tavassoly, I. A Systems Biology Roadmap to Decode mTOR Control System in Cancer. *Interdiscip. Sci.* **2020**, *12*, 1–11. [[CrossRef](#)] [[PubMed](#)]
142. Preau, S.; Ambler, M.; Sigurta, A.; Kleyman, A.; Dyson, A.; Hill, N.E.; Boulanger, E.; Singer, M. Protein recycling and limb muscle recovery after critical illness in slow- and fast-twitch limb muscle. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2019**. [[CrossRef](#)] [[PubMed](#)]
143. Dong, W.; Wang, R.; Ma, L.N.; Xu, B.L.; Zhang, J.S.; Zhao, Z.W.; Wang, Y.L.; Zhang, X. Influence of age-related learning and memory capacity of mice: Different effects of a high and low caloric diet. *Aging Clin. Exp. Res.* **2016**, *28*, 303–311. [[CrossRef](#)]
144. Maiese, K. Forkhead transcription factors: New considerations for alzheimer's disease and dementia. *J. Transl. Sci.* **2016**, *2*, 241–247. [[CrossRef](#)]
145. Min, J.J.; Huo, X.L.; Xiang, L.Y.; Qin, Y.Q.; Chai, K.Q.; Wu, B.; Jin, L.; Wang, X.T. Protective effect of DI-3n-butylphthalide on learning and memory impairment induced by chronic intermittent hypoxia-hypercapnia exposure. *Sci. Rep.* **2014**, *4*, 5555. [[CrossRef](#)] [[PubMed](#)]
146. Zhang, Z.H.; Wu, Q.Y.; Zheng, R.; Chen, C.; Chen, Y.; Liu, Q.; Hoffmann, P.R.; Ni, J.Z.; Song, G.L. Selenomethionine mitigates cognitive decline by targeting both tau hyperphosphorylation and autophagic clearance in an Alzheimer's disease mouse model. *J. Neurosci.* **2017**, *37*, 2449–2462. [[CrossRef](#)] [[PubMed](#)]
147. Rashidi, S.; Mansouri, R.; Ali-Hassanzadeh, M.; Mojtahedi, Z.; Shafiei, R.; Savardashtaki, A.; Hamidizadeh, N.; Karimazar, M.; Nguewa, P.; Manzano-Román, R. The host mTOR pathway and parasitic diseases pathogenesis. *Parasitol. Res.* **2021**, *120*, 1151–1166. [[CrossRef](#)] [[PubMed](#)]
148. Evans, T.; Kok, W.L.; 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 Res.* **2018**, *1681*, 1–13. [[CrossRef](#)] [[PubMed](#)]
149. 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. *Sci. Rep.* **2015**, *5*, 12115. [[CrossRef](#)]
150. Beker, M.C.; Caglayan, B.; Yalcin, E.; Caglayan, A.B.; Turkseven, S.; Gurel, B.; Kelestemur, T.; Sertel, E.; Sahin, Z.; Kutlu, S.; et al. Time-of-Day Dependent Neuronal Injury after Ischemic Stroke: Implication of Circadian Clock Transcriptional Factor Bmal1 and Survival Kinase AKT. *Mol. Neurobiol.* **2018**, *55*, 2565–2576. [[CrossRef](#)]
151. Chen, B.; Tan, Y.; Liang, Y.; Li, Y.; Chen, L.; Wu, S.; Xu, W.; Wang, Y.; Zhao, W.; Wu, J. Per2 participates in AKT-mediated drug resistance in A549/DDP lung adenocarcinoma cells. *Oncol. Lett.* **2017**, *13*, 423–428. [[CrossRef](#)]
152. Ramanathan, C.; Kathale, N.D.; Liu, D.; Lee, C.; Freeman, D.A.; Hogenesch, J.B.; Cao, R.; Liu, A.C. mTOR signaling regulates central and peripheral circadian clock function. *PLoS Genet.* **2018**, *14*, e1007369. [[CrossRef](#)]
153. Chen, L.; Zhang, Y.; Li, D.; Zhang, N.; Liu, R.; Han, B.; Wei, C.; Liu, H.; Xu, X.; Hao, J. Everolimus (RAD001) ameliorates vascular cognitive impairment by regulating microglial function via the mTORC1 signaling pathway. *J. Neuroimmunol.* **2016**, *299*, 164–171. [[CrossRef](#)]
154. Chung, C.L.; Lawrence, I.; Hoffman, M.; Elgindi, D.; Nadhan, K.; Potnis, M.; Jin, A.; Sershon, C.; Binnebose, R.; Lorenzini, A.; et al. Topical rapamycin reduces markers of senescence and aging in human skin: An exploratory, prospective, randomized trial. *Geroscience* **2019**, *41*, 6. [[CrossRef](#)]
155. Park, J.A.; Lee, C.H. Temporal changes in mammalian target of rapamycin (mTOR) and phosphorylated-mTOR expressions in the hippocampal CA1 region of rat with vascular dementia. *J. Vet. Sci.* **2017**, *18*, 11–16. [[CrossRef](#)]
156. An, X.; Yao, X.; Li, B.; Yang, W.; Cui, R.; Zhao, G.; Jin, Y. Role of BDNF-mTORC1 Signaling Pathway in Female Depression. *Neural Plast.* **2021**, *2021*, 6619515. [[CrossRef](#)] [[PubMed](#)]

157. Damstra-Oddy, J.L.; Warren, E.C.; Perry, C.J.; Desfougères, Y.; Fitzpatrick, J.K.; Schaf, J.; Costelloe, L.; Hind, W.; Downer, E.J.; Saiardi, A.; et al. Phytocannabinoid-dependent mTORC1 regulation is dependent upon inositol polyphosphate multikinase activity. *Br. J. Pharmacol.* **2021**, *178*, 1149–1163. [[CrossRef](#)] [[PubMed](#)]
158. Hwang, S.K.; Kim, H.H. The functions of mTOR in ischemic diseases. *BMB Rep.* **2011**, *44*, 506–511. [[CrossRef](#)] [[PubMed](#)]
159. Maiese, K. Erythropoietin and mTOR: A “One-Two Punch” for Aging-Related Disorders Accompanied by Enhanced Life Expectancy. *Curr. Neurovasc. Res.* **2016**, *13*, 329–340. [[CrossRef](#)] [[PubMed](#)]
160. Martinez de Morentin, P.B.; Martinez-Sanchez, N.; Roa, J.; Ferno, J.; Nogueiras, R.; Tena-Sempere, M.; Dieguez, C.; Lopez, M. Hypothalamic mTOR: The rookie energy sensor. *Curr. Mol. Med.* **2014**, *14*, 3–21. [[CrossRef](#)] [[PubMed](#)]
161. Maiese, K. Sirtuins in Metabolic Disease: Innovative Therapeutic Strategies with SIRT1, AMPK, mTOR, and Nicotinamide. In *Sirtuin Biology in Cancer and Metabolic Disease: Cellular Pathways for Clinical Discovery*; Maiese, K., Ed.; Academic Press: Cambridge, MA, USA; Elsevier: Amsterdam, The Netherlands, 2021; ISBN 9780128141182.
162. Maiese, K. Targeting the core of neurodegeneration: FoxO, mTOR, and SIRT1. *Neural Regen. Res.* **2021**, *16*, 448–455. [[CrossRef](#)] [[PubMed](#)]
163. Xu, T.; Liu, J.; Li, X.R.; Yu, Y.; Luo, X.; Zheng, X.; Cheng, Y.; Yu, P.Q.; Liu, Y. The mTOR/NF- κ B Pathway Mediates Neuroinflammation and Synaptic Plasticity in Diabetic Encephalopathy. *Mol. Neurobiol.* **2021**. [[CrossRef](#)]
164. Johri, M.K.; Lashkari, H.V.; Gupta, D.; Vedagiri, D.; Harshan, K.H. mTORC1 restricts hepatitis C virus RNA replication through ULK1-mediated suppression of miR-122 and facilitates post-replication events. *J. Gen. Virol.* **2020**, *101*, 86–95. [[CrossRef](#)]
165. Maiese, K. Driving neural regeneration through the mammalian target of rapamycin. *Neural Regen. Res.* **2014**, *9*, 1413–1417. [[CrossRef](#)]
166. Malla, R.; Ashby, C.R., Jr.; Narayanan, N.K.; Narayanan, B.; Faridi, J.S.; Tiwari, A.K. Proline-rich AKT substrate of 40-kDa (PRAS40) in the pathophysiology of cancer. *Biochem. Biophys. Res. Commun.* **2015**, *463*, 161–166. [[CrossRef](#)]
167. Hasbal, N.B.; 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. *Ann. Transplant.* **2021**, *26*, e929279. [[CrossRef](#)]
168. Patocka, J.; Kuca, K.; Oleksak, P.; Nepovimova, E.; Valis, M.; Novotny, M.; Klimova, B. Rapamycin: Drug Repurposing in SARS-CoV-2 Infection. *Pharmaceuticals* **2021**, *14*, 217. [[CrossRef](#)]
169. Pereira, G.; Leão, A.; Erustes, A.G.; Morais, I.B.M.; Vrechi, T.A.M.; Zamarioli, L.D.S.; Pereira, C.A.S.; Marchioro, L.O.; Sperandio, L.P.; Lins, Í.V.F.; et al. Pharmacological Modulators of Autophagy as a Potential Strategy for the Treatment of COVID-19. *Int. J. Mol. Sci.* **2021**, *22*, 4067. [[CrossRef](#)]
170. Shi, G.; Chiramel, A.I.; Majdoul, S.; Lai, K.K.; Das, S.; Beare, P.A.; Andresson, T.; Best, S.M.; Compton, A.A. Rapalogs downmodulate intrinsic immunity and promote cell entry of SARS-CoV-2. *bioRxiv* **2021**. [[CrossRef](#)]
171. Querfurth, H.; Lee, H.K. Mammalian/mechanistic target of rapamycin (mTOR) complexes in neurodegeneration. *Mol. Neurodegener.* **2021**, *16*, 44. [[CrossRef](#)] [[PubMed](#)]
172. Chong, Z.Z.; Shang, Y.C.; Wang, S.; Maiese, K. Shedding new light on neurodegenerative diseases through the mammalian target of rapamycin. *Prog. Neurobiol.* **2012**, *99*, 128–148. [[CrossRef](#)] [[PubMed](#)]
173. Huang, D.; Shen, S.; Cai, M.; Jin, L.; Lu, J.; Xu, K.; Zhang, J.; Feng, G.; Hu, Y.; Zheng, K.; et al. Role of mTOR complex in IGF-1 induced neural differentiation of DPSCs. *J. Mol. Histol.* **2019**. [[CrossRef](#)] [[PubMed](#)]
174. Jacinto, E.; Loewith, R.; Schmidt, A.; Lin, S.; Ruegg, M.A.; Hall, A.; Hall, M.N. Mammalian TOR complex 2 controls the actin cytoskeleton and is rapamycin insensitive. *Nat. Cell Biol.* **2004**, *6*, 1122–1128. [[CrossRef](#)]
175. 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. *Front. Aging Neurosci.* **2019**, *11*, 314. [[CrossRef](#)]
176. Sharma, S.K.; Ebadi, M. Metallothionein attenuates 3-morpholinopyridone (SIN-1)-induced oxidative stress in dopaminergic neurons. *Antioxid. Redox Signal.* **2003**, *5*, 251–264. [[CrossRef](#)]
177. Vishwas, D.K.; Mukherjee, A.; Haldar, C.; Dash, D.; Nayak, M.K. Improvement of oxidative stress and immunity by melatonin: An age dependent study in golden hamster. *Exp. Gerontol.* **2013**, *48*, 168–182. [[CrossRef](#)]
178. Zhang, G.Z.; Deng, Y.J.; Xie, Q.Q.; Ren, E.H.; Ma, Z.J.; He, X.G.; Gao, Y.C.; Kang, X.W. Sirtuins and intervertebral disc degeneration: Roles in inflammation, oxidative stress, and mitochondrial function. *Clin. Chim. Acta* **2020**, *508*, 33–42. [[CrossRef](#)]
179. Sato, S.; Solanas, G.; Peixoto, F.O.; Bee, L.; Symeonidi, A.; Schmidt, M.S.; Brenner, C.; Masri, S.; Benitah, S.A.; Sassone-Corsi, P. Circadian Reprogramming in the Liver Identifies Metabolic Pathways of Aging. *Cell* **2017**, *170*, 664–677.e611. [[CrossRef](#)]
180. Charles, S.; Raj, V.; Arokiaraj, J.; Mala, K. Caveolin1/protein arginine methyltransferase1/sirtuin1 axis as a potential target against endothelial dysfunction. *Pharmacol. Res.* **2017**, *119*, 1–11. [[CrossRef](#)]
181. Chong, Z.Z.; Shang, Y.C.; Wang, S.; Maiese, K. SIRT1: New avenues of discovery for disorders of oxidative stress. *Expert Opin. Ther. Targets* **2012**, *16*, 167–178. [[CrossRef](#)]
182. Cui, L.; Guo, J.; Zhang, Q.; Yin, J.; Li, J.; Zhou, W.; Zhang, T.; Yuan, H.; Zhao, J.; Zhang, L.; et al. Erythropoietin activates SIRT1 to protect human cardiomyocytes against doxorubicin-induced mitochondrial dysfunction and toxicity. *Toxicol. Lett.* **2017**, *275*, 28–38. [[CrossRef](#)]
183. Geng, C.; Xu, H.; Zhang, Y.; Gao, Y.; Li, M.; Liu, X.; Gao, M.; Wang, X.; Liu, X.; Fang, F.; et al. Retinoic acid ameliorates high-fat diet-induced liver steatosis through sirt1. *Sci. China Life Sci.* **2017**, *60*, 1234–1241. [[CrossRef](#)] [[PubMed](#)]

184. Maiese, K. SIRT1 and stem cells: In the forefront with cardiovascular disease, neurodegeneration and cancer. *World J. Stem Cells* **2015**, *7*, 235–242. [[CrossRef](#)] [[PubMed](#)]
185. Maiese, K. Harnessing the Power of SIRT1 and Non-coding RNAs in Vascular Disease. *Curr. Neurovasc. Res.* **2017**, *14*, 82–88. [[CrossRef](#)] [[PubMed](#)]
186. Maulik, M.; Mitra, S.; Hunter, S.; Hunstiger, M.; Oliver, S.R.; Bult-Ito, A.; Taylor, B.E. Sir-2.1 mediated attenuation of alpha-synuclein expression by Alaskan bog blueberry polyphenols in a transgenic model of *Caenorhabditis elegans*. *Sci. Rep.* **2018**, *8*, 10216. [[CrossRef](#)] [[PubMed](#)]
187. Sooknual, P.; Pindaew, R.; Phopin, K.; Ruankham, W.; Prachayasittikul, S.; Ruchirawat, S.; Prachayasittikul, V. Synthesis and neuroprotective effects of novel chalcone-triazole hybrids. *Bioorg. Chem.* **2020**, *105*, 104384. [[CrossRef](#)]
188. Maiese, K. Prospects and Perspectives for WISP1 (CCN4) in Diabetes Mellitus. *Curr. Neurovasc. Res.* **2020**, *17*, 327–331. [[CrossRef](#)]
189. Wang, N.; Luo, Z.; Jin, M.; Sheng, W.; Wang, H.T.; Long, X.; Wu, Y.; Hu, P.; Xu, H.; Zhang, X. Exploration of age-related mitochondrial dysfunction and the anti-aging effects of resveratrol in zebrafish retina. *Aging* **2019**, *11*, 3117–3137. [[CrossRef](#)]
190. Wang, Y.; Gao, S.; Zheng, V.; Chen, L.; Ma, M.; Shen, S.; Qu, J.; Zhang, H.; Gurney, M.E.; O'Donnell, J.M.; et al. A Novel PDE4D Inhibitor BPN14770 Reverses Scopolamine-Induced Cognitive Deficits via cAMP/SIRT1/Akt/Bcl-2 Pathway. *Front. Cell Dev. Biol.* **2020**, *8*, 599389. [[CrossRef](#)]
191. Yang, J.; Suo, H.; Song, J. Protective role of mitoquinone against impaired mitochondrial homeostasis in metabolic syndrome. *Crit. Rev. Food Sci. Nutr.* **2020**, *20*, 1–19. [[CrossRef](#)] [[PubMed](#)]
192. Zhang, H.; Yang, X.; Pang, X.; Zhao, Z.; Yu, H.; Zhou, H. Genistein protects against ox-LDL-induced senescence through enhancing SIRT1/LKB1/AMPK-mediated autophagy flux in HUVECs. *Mol. Cell Biochem.* **2019**, *455*, 127–134. [[CrossRef](#)] [[PubMed](#)]
193. Maiese, K.; Chong, Z.Z.; Shang, Y.C. OutFOXing disease and disability: The therapeutic potential of targeting FoxO proteins. *Trends Mol. Med.* **2008**, *14*, 219–227. [[CrossRef](#)] [[PubMed](#)]
194. BinMowyna, M.N.; AlFaris, N.A. Kaempferol suppresses acetaminophen-induced liver damage by upregulation/activation of SIRT1. *Pharm. Biol.* **2021**, *59*, 146–156. [[CrossRef](#)] [[PubMed](#)]
195. Rong, Y.; Ren, J.; Song, W.; Xiang, R.; Ge, Y.; Lu, W.; Fu, T. Resveratrol Suppresses Severe Acute Pancreatitis-Induced Microcirculation Disturbance through Targeting SIRT1-FOXO1 Axis. *Oxidative Med. Cell. Longev.* **2021**, *2021*, 8891544. [[CrossRef](#)] [[PubMed](#)]
196. Shati, A.A.; El-Kott, A.F. Acylated ghrelin protects against Doxorubicin-induced nephropathy by activating SIRT1. *Basic Clin. Pharmacol. Toxicol.* **2021**. [[CrossRef](#)] [[PubMed](#)]
197. Yaman, D.; Takmaz, T.; Yüksel, N.; Dinçer, S.A.; Şahin, F. Evaluation of silent information regulator T (SIRT) 1 and Forkhead Box O (FOXO) transcription factor 1 and 3a genes in glaucoma. *Mol. Biol. Rep.* **2020**. [[CrossRef](#)]
198. Maiese, K.; Chong, Z.Z.; Shang, Y.C.; Hou, J. FoxO proteins: Cunning concepts and considerations for the cardiovascular system. *Clin. Sci.* **2009**, *116*, 191–203. [[CrossRef](#)] [[PubMed](#)]
199. Sanphui, P.; Das, A.K.; Biswas, S.C. FoxO3a requires BAF57, a subunit of chromatin remodeler SWI/SNF complex for induction of PUMA in a model of Parkinson's disease. *J. Neurochem.* **2020**, *154*, e14969. [[CrossRef](#)]
200. 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. *J. Neurosci.* **2014**, *34*, 7917–7930. [[CrossRef](#)] [[PubMed](#)]
201. Maiese, K. Novel Insights for Multiple Sclerosis and Demyelinating Disorders with Apoptosis, Autophagy, FoxO, and mTOR. *Curr. Neurovasc. Res.* **2021**, *18*, 1–4. [[CrossRef](#)] [[PubMed](#)]
202. Gökdoğan Edgünlü, T.; Ünal, Y.; Karakaş 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. [[CrossRef](#)] [[PubMed](#)]
203. Saleem, S.; Biswas, S.C. Tribbles Pseudokinase 3 Induces Both Apoptosis and Autophagy in Amyloid-beta-induced Neuronal Death. *J. Biol. Chem.* **2017**, *292*, 2571–2585. [[CrossRef](#)] [[PubMed](#)]
204. Tabibzadeh, S. Signaling pathways and effectors of aging. *Front. Biosci.* **2021**, *26*, 50–96. [[CrossRef](#)]
205. Liu, X.L.; Gao, C.C.; Qi, M.; Han, Y.L.; Zhou, M.L.; Zheng, L.R. Expression of FOXO transcription factors in the brain following traumatic brain injury. *Neurosci. Lett.* **2021**, *753*, 135882. [[CrossRef](#)]
206. Maiese, K. Novel Treatment Strategies for Neurodegenerative Disease with Sirtuins. In *Sirtuin Biology in Medicine: Targeting New Avenues of Care in Development, Aging, and Disease*; Academic Press: Cambridge, MA, USA; Elsevier: Amsterdam, The Netherlands, 2021; ISBN 9780128224670.
207. Xiong, S.; Salazar, G.; Patrushev, N.; Alexander, R.W. FoxO1 Mediates an Autofeedback Loop Regulating SIRT1 Expression. *J. Biol. Chem.* **2011**, *286*, 5289–5299. [[CrossRef](#)] [[PubMed](#)]
208. Lin, C.L.; Huang, W.N.; Li, H.H.; Huang, C.N.; Hsieh, S.; Lai, C.; Lu, F.J. 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. *Chem. Biol. Interact.* **2015**, *240*, 12–21. [[CrossRef](#)] [[PubMed](#)]
209. Guo, P.; Wang, D.; Wang, X.; Feng, H.; Tang, Y.; Sun, R.; Zheng, Y.; Dong, L.; Zhao, J.; Zhang, X.; et al. Effect and mechanism of fuzhisan and donepezil on the sirtuin 1 pathway and amyloid precursor protein metabolism in PC12 cells. *Mol. Med. Rep.* **2016**, *13*, 3539–3546. [[CrossRef](#)]
210. Joe, Y.; Chen, Y.; Park, J.; Kim, H.J.; Rah, S.Y.; Ryu, J.; Cho, G.J.; Choi, H.S.; Ryter, S.W.; Park, J.W.; et al. Cross-talk between CD38 and TTP Is Essential for Resolution of Inflammation during Microbial Sepsis. *Cell Rep.* **2020**, *30*, 1063–1076.e1065. [[CrossRef](#)] [[PubMed](#)]

211. Pan, Y.R.; Song, J.Y.; Fan, B.; Wang, Y.; Che, L.; Zhang, S.M.; Chang, Y.X.; He, C.; Li, G.Y. mTOR may interact with PARP-1 to regulate visible light-induced parthanatos in photoreceptors. *Cell Commun. Signal.* **2020**, *18*, 27. [[CrossRef](#)]
212. Wang, R.H.; Kim, H.S.; Xiao, C.; Xu, X.; Gavrilova, O.; Deng, C.X. Hepatic Sirt1 deficiency in mice impairs mTORC2/Akt signaling and results in hyperglycemia, oxidative damage, and insulin resistance. *J. Clin. Investig.* **2011**, *121*, 4477–4490. [[CrossRef](#)]
213. Yin, Q.; Wang, J.F.; Xu, X.H.; Xie, H. Effect of lycopene on pain facilitation and the SIRT1/mTOR pathway in the dorsal horn of burn injury rats. *Eur. J. Pharmacol.* **2020**, 173365. [[CrossRef](#)]
214. Maiese, K. MicroRNAs and SIRT1: A Strategy for Stem Cell Renewal and Clinical Development? *J. Transl. Sci.* **2015**, *1*, 55–57. [[CrossRef](#)]
215. Mu, N.; Lei, Y.; Wang, Y.; Wang, Y.; Duan, Q.; Ma, G.; Liu, X.; Su, L. 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. [[CrossRef](#)]
216. Shen, C.; Dou, X.; Ma, Y.; Ma, W.; Li, S.; Song, Z. Nicotinamide protects hepatocytes against palmitate-induced lipotoxicity via SIRT1-dependent autophagy induction. *Nutr. Res.* **2017**, *40*, 40–47. [[CrossRef](#)]
217. Guo, W.; Qian, L.; Zhang, J.; Zhang, W.; Morrison, A.; Hayes, P.; Wilson, S.; Chen, T.; Zhao, J. Sirt1 overexpression in neurons promotes neurite outgrowth and cell survival through inhibition of the mTOR signaling. *J. Neurosci. Res.* **2011**, *89*, 1723–1736. [[CrossRef](#)] [[PubMed](#)]
218. Ou, X.; Lee, M.R.; Huang, X.; Messina-Graham, S.; Broxmeyer, H.E. SIRT1 positively regulates autophagy and mitochondria function in embryonic stem cells under oxidative stress. *Stem Cells* **2014**, *32*, 1183–1194. [[CrossRef](#)] [[PubMed](#)]
219. Pal, P.B.; Sonowal, H.; Shukla, K.; Srivastava, S.K.; Ramana, K.V. Aldose reductase regulates hyperglycemia-induced HUVEC death via SIRT1/AMPK-alpha1/mTOR pathway. *J. Mol. Endocrinol.* **2019**, *63*, 11–25. [[CrossRef](#)] [[PubMed](#)]
220. Zhang, C.; Li, C.; Chen, S.; Li, Z.; Ma, L.; Jia, X.; Wang, K.; Bao, J.; Liang, Y.; Chen, M.; et al. Hormetic effect of panaxatriol saponins confers neuroprotection in PC12 cells and zebrafish through PI3K/AKT/mTOR and AMPK/SIRT1/FOXO3 pathways. *Sci. Rep.* **2017**, *7*, 41082. [[CrossRef](#)]
221. Caton, P.W.; Kieswich, J.; Yaqoob, M.M.; Holness, M.J.; Sugden, M.C. 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 Obes. Metab.* **2011**, *13*, 1097–1104. [[CrossRef](#)]
222. Oblong, J.E. The evolving role of the NAD⁺/nicotinamide metabolome in skin homeostasis, cellular bioenergetics, and aging. *DNA Repair* **2014**, *23*, 59–63. [[CrossRef](#)]
223. Zhang, Y.; Zhu, X.; Wang, G.; Chen, L.; Yang, H.; He, F.; Lin, J. Melatonin Rescues the Ti Particle-Impaired Osteogenic Potential of Bone Marrow Mesenchymal Stem Cells via the SIRT1/SOD2 Signaling Pathway. *Calcif. Tissue Int.* **2020**, *107*, 474–488. [[CrossRef](#)]
224. 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. [[CrossRef](#)]
225. Hou, J.; Wang, S.; Shang, Y.C.; Chong, Z.Z.; Maiese, K. Erythropoietin Employs Cell Longevity Pathways of SIRT1 to Foster Endothelial Vascular Integrity During Oxidant Stress. *Curr. Neurovasc. Res.* **2011**, *8*, 220–235. [[CrossRef](#)] [[PubMed](#)]
226. Wang, L.; Teng, R.; Di, L.; Rogers, H.; Wu, H.; Kopp, J.B.; Noguchi, C.T. 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. [[CrossRef](#)]
227. Wu, H.; Wang, H.; Zhang, W.; Wei, X.; Zhao, J.; Yan, P.; Liu, C. rhEPO affects apoptosis in hippocampus of aging rats by upregulating SIRT1. *Int. J. Clin. Exp. Pathol.* **2015**, *8*, 6870–6880. [[PubMed](#)]
228. Maiese, K.; Li, F.; Chong, Z.Z. New avenues of exploration for erythropoietin. *JAMA* **2005**, *293*, 90–95. [[CrossRef](#)]
229. Maiese, K. Regeneration in the nervous system with erythropoietin. *Front. Biosci.* **2016**, *21*, 561–596. [[CrossRef](#)]
230. Maiese, K. Erythropoietin and diabetes mellitus. *World J. Diabetes* **2015**, *6*, 1259–1273. [[CrossRef](#)]
231. Maiese, K.; Chong, Z.Z.; Shang, Y.C. Raves and risks for erythropoietin. *Cytokine Growth Factor Rev.* **2008**, *19*, 145–155. [[CrossRef](#)]
232. Ezenwa, B.; Ezeaka, C.; Fajolu, I.; Ogbenna, A.; Olowoyeye, O.; Nwaiwu, O.; Opoola, Z.; Olorunfemi, G. Impact of Erythropoietin in the management of Hypoxic Ischaemic Encephalopathy in resource-constrained settings: Protocol for a randomized control trial. *BMC Neurol.* **2020**, *20*, 171. [[CrossRef](#)] [[PubMed](#)]
233. Govindappa, P.K.; Talukder, M.A.H.; Gurjar, A.A.; Hegarty, J.P.; Elfar, J.C. An effective erythropoietin dose regimen protects against severe nerve injury-induced pathophysiological changes with improved neural gene expression and enhances functional recovery. *Int. Immunopharmacol.* **2020**, *82*, 106330. [[CrossRef](#)]
234. 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*, 424. [[CrossRef](#)] [[PubMed](#)]
235. Inkster, B.; Zai, G.; Lewis, G.; Miskowiak, K.W. GSK3beta: A plausible mechanism of cognitive and hippocampal changes induced by erythropoietin treatment in mood disorders? *Transl. Psychiatry* **2018**, *8*, 216. [[CrossRef](#)]
236. Liu, W.; Varier, K.M.; Sample, K.M.; Zacksenhaus, E.; Gajendran, B.; Ben-David, Y. Erythropoietin Signaling in the Microenvironment of Tumors and Healthy Tissues. *Adv. Exp. Med. Biol.* **2020**, *1223*, 17–30. [[CrossRef](#)]
237. Negri, S.; Faris, P.; Rosti, V.; Antognazza, M.R.; Lodola, F.; Moccia, F. Endothelial TRPV1 as an Emerging Molecular Target to Promote Therapeutic Angiogenesis. *Cells* **2020**, *9*, 1341. [[CrossRef](#)] [[PubMed](#)]

238. Tang, Z.; Yang, G.; Wang, X.; Chen, F.; Liao, Z.; Zhang, Z.; Liu, Z.; Zeng, W.; Fang, M.; Wang, W.; et al. AKT/GSK-3 β / β -catenin signaling pathway participates in erythropoietin-promoted glioma proliferation. *J. Neurooncol.* **2020**, *149*, 231–242. [[CrossRef](#)] [[PubMed](#)]
239. Caprara, C.; Grimm, C. From oxygen to erythropoietin: Relevance of hypoxia for retinal development, health and disease. *Prog. Retin. Eye Res.* **2012**, *31*, 89–119. [[CrossRef](#)]
240. Maiese, K. Triple play: Promoting neurovascular longevity with nicotinamide, WNT, and erythropoietin in diabetes mellitus. *Biomed. Pharmacother.* **2008**, *62*, 218–232. [[CrossRef](#)]
241. Entezari, M.; Flavarjani, Z.K.; Ramezani, A.; Nikkhah, H.; Karimi, S.; Moghadam, H.F.; Daftarian, N.; Yaseri, M. Combination of intravitreal bevacizumab and erythropoietin versus intravitreal bevacizumab alone for refractory diabetic macular edema: A randomized double-blind clinical trial. *Graefes Arch. Clin. Exp. Ophthalmol.* **2019**. [[CrossRef](#)]
242. Montesano, A.; Bonfigli, A.R.; De Luca, M.; Crocco, P.; Garagnani, P.; Marasco, E.; Pirazzini, C.; Giuliani, C.; Romagnoli, F.; Franceschi, C.; et al. Erythropoietin (EPO) haplotype associated with all-cause mortality in a cohort of Italian patients with Type-2 Diabetes. *Sci. Rep.* **2019**, *9*, 10395. [[CrossRef](#)]
243. Chong, Z.Z.; Kang, J.Q.; Maiese, K. Erythropoietin is a novel vascular protectant through activation of Akt1 and mitochondrial modulation of cysteine proteases. *Circulation* **2002**, *106*, 2973–2979. [[CrossRef](#)] [[PubMed](#)]
244. Chong, Z.Z.; Kang, J.Q.; Maiese, K. Erythropoietin fosters both intrinsic and extrinsic neuronal protection through modulation of microglia, Akt1, Bad, and caspase-mediated pathways. *Br. J. Pharmacol.* **2003**, *138*, 1107–1118. [[CrossRef](#)] [[PubMed](#)]
245. Shang, Y.C.; Chong, Z.Z.; Wang, S.; Maiese, K. Prevention of beta-amyloid degeneration of microglia by erythropoietin depends on Wnt1, the PI 3-K/mTOR pathway, Bad, and Bcl-xL. *Aging* **2012**, *4*, 187–201. [[CrossRef](#)]
246. Chong, Z.Z.; Shang, Y.C.; Wang, S.; Maiese, K. PRAS40 Is an Integral Regulatory Component of Erythropoietin mTOR Signaling and Cytoprotection. *PLoS ONE* **2012**, *7*, e45456. [[CrossRef](#)]
247. Chong, Z.Z.; Lin, S.H.; Kang, J.Q.; Maiese, K. Erythropoietin prevents early and late neuronal demise through modulation of Akt1 and induction of caspase 1, 3, and 8. *J. Neurosci. Res.* **2003**, *71*, 659–669. [[CrossRef](#)] [[PubMed](#)]
248. Kwon, M.S.; Kim, M.H.; Kim, S.H.; Park, K.D.; Yoo, S.H.; Oh, I.U.; Pak, S.; Seo, Y.J. Erythropoietin exerts cell protective effect by activating PI3K/Akt and MAPK pathways in C6 Cells. *Neurol. Res.* **2014**, *36*, 215–223. [[CrossRef](#)]
249. Wang, G.B.; Ni, Y.L.; Zhou, X.P.; Zhang, W.F. The AKT/mTOR pathway mediates neuronal protective effects of erythropoietin in sepsis. *Mol. Cell. Biochem.* **2014**, *385*, 125–132. [[CrossRef](#)]
250. Jang, W.; Kim, H.J.; Li, H.; Jo, K.D.; Lee, M.K.; Yang, H.O. The Neuroprotective Effect of Erythropoietin on Rotenone-Induced Neurotoxicity in SH-SY5Y Cells Through the Induction of Autophagy. *Mol. Neurobiol.* **2015**, *53*, 3812–3821. [[CrossRef](#)]
251. Maiese, K. Warming Up to New Possibilities with the Capsaicin Receptor TRPV1: mTOR, AMPK, and Erythropoietin. *Curr. Neurovasc. Res.* **2017**, *14*, 184–189. [[CrossRef](#)]
252. Yu, Y.; Shiou, S.R.; Guo, Y.; Lu, L.; Westerhoff, M.; Sun, J.; Petrof, E.O.; Claud, E.C. Erythropoietin protects epithelial cells from excessive autophagy and apoptosis in experimental neonatal necrotizing enterocolitis. *PLoS ONE* **2013**, *8*, e69620. [[CrossRef](#)]
253. Shang, Y.C.; Chong, Z.Z.; Wang, S.; Maiese, K. Erythropoietin and Wnt1 Govern Pathways of mTOR, Apaf-1, and XIAP in Inflammatory Microglia. *Curr. Neurovasc. Res.* **2011**, *8*, 270–285. [[CrossRef](#)] [[PubMed](#)]
254. Shang, Y.C.; Chong, Z.Z.; Wang, S.; Maiese, K. WNT1 Inducible Signaling Pathway Protein 1 (WISP1) Targets PRAS40 to Govern beta-Amyloid Apoptotic Injury of Microglia. *Curr. Neurovasc. Res.* **2012**, *9*, 239–249. [[CrossRef](#)] [[PubMed](#)]
255. 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. *Hum. Cell* **2019**, *32*, 275–284. [[CrossRef](#)] [[PubMed](#)]