HHS Public Access

Author manuscript

Curr Neurovasc Res. Author manuscript; available in PMC 2017 September 16.

Published in final edited form as:

Curr Neurovasc Res. 2017 ; 14(3): 299–304. doi:10.2174/1567202614666170718092010.

Moving to the Rhythm with Clock (Circadian) Genes, Autophagy, mTOR, and SIRT1 in Degenerative Disease and Cancer

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Abstract

Background—The mammalian circadian clock and its associated clock genes are increasingly be recognized as critical components for a number of physiological and disease processes that extend beyond hormone release, thermal regulation, and sleep-wake cycles. New evidence suggests that clinical behavior disruptions that involve prolonged shift work and even space travel may negatively impact circadian rhythm and lead to multi-system disease.

Methods—In light of the significant role circadian rhythm can hold over the body's normal physiology as well as disease processes, we examined and discussed the impact circadian rhythm and clock genes hold over lifespan, neurodegenerative disorders, and tumorigenesis.

Results—In experimental models, lifespan is significantly reduced with the introduction of arrhythmic mutants and leads to an increase in oxidative stress exposure. Interestingly, patients with Alzheimer's disease and Parkinson's disease may suffer disease onset or progression as a result of alterations in the DNA methylation of clock genes as well as prolonged pharmacological treatment for these disorders that may lead to impairment of circadian rhythm function. Tumorigenesis also can occur with the loss of a maintained circadian rhythm and lead to an increased risk for nasopharyngeal carcinoma, breast cancer, and metastatic colorectal cancer. Interestingly, the circadian clock system relies upon the regulation of the critical pathways of autophagy, the mechanistic target of rapamycin (mTOR), AMP activated protein kinase (AMPK), and silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1) as well as proliferative mechanisms that involve the *wingless* pathway of Wnt/β-catenin pathway to foster cell survival during injury and block tumor cell growth.

Conclusions—Future targeting of the pathways of autophagy, mTOR, SIRT1, and Wnt that control mammalian circadian rhythm may hold the key for the development of novel and effective therapies against aging- related disorders, neurodegenerative disease, and tumorigenesis.

Keywords

aging; aging-related disorders; Alzheimer's disease; AMP activated protein kinase (AMPK); angiogenesis; apoptosis; autophagy; BMAL1; cardiovascular disease; β-catenin; circadian rhythm; CLOCK; clock genes; Cryptochrome; diabetes mellitus; hamartin (tuberous sclerosis 1)/tuberin (tuberous sclerosis 2) (TSC1/TSC2); Huntington's disease; mechanistic target of rapamycin (mTOR); mTOR Complex 1 (mTORC1); mTOR Complex 2 (mTORC2); metabolism; nerve

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Competing Interests: There are no conflicts of interest to declare.

growth factor; nicotinamide; nicotinamide adenine dinucleotide (NAD^+); Parkinson's disease; period (PER); oxidative stress; programmed cell death; REV-ERBα; RORα; RORE; shift work; silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1); sirtuin; space travel; stem cells; suprachiasmatic nucleus; wingless; Wnt

Circadian Rhythm and Clock Genes

The mammalian circadian clock is located in the suprachiasmatic nucleus (SCN) that lies above the optic chiasm to receive light input from photosensitive ganglion cells in the retina. The SCN relies upon the pineal gland, hypothalamic nuclei, and vasoactive intestinal peptide to control multiple process such as the release of hormones cortisol and melatonin, oxidative stress responses (1), and the regulation of body temperature in the circadian cycle (2-4).

The circadian clock relies upon cellular signals and light input to align itself with solar time and oscillate over a twenty-four hour period. This clock receives daily cues from external environmental sources that consist of daylight and darkness to drive circadian rhythm. Ultimately, the circadian rhythm controls behavior, normal physiology, and cellular biochemical transmission in an organism.

Members of the basic helix-loop-helix -PAS (Period-Arnt-Single-minded) transcription factor family, such as CLOCK and BMAL1 (5), oversee the expression of the genes *Cryptochrome (Cry1 and Cry2)* and *Period (Per1, Per2, and Per3).* Negative feedback is provided by PER:CRY heterodimers that can translocate to the nucleus to block the transcription of CLOCK:BMAL1 complexes. Additional regulatory loops consist of the activation by CLOCK:BMAL1 heterodimers of retinoic acid-related orphan nuclear receptors REV-ERBα and RORα. These receptors bind retinoic acid-related orphan receptor response elements (ROREs) present in the BMAL1 promoter to control transcription with RORs activating transcription and REV-ERBs repressing transcription to lead to a circadian oscillation of BMAL1 (6, 7).

Circadian Rhythm in Degenerative Disease and Cancer

Neurodegenerative diseases and decreased lifespan have been linked to the function of the mammalian circadian clock. In studies with *Drosophila melanogaster*, lifespan was reduced in three arrhythmic mutants involving ClkAR, cyc0 and tim0. In particular, 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 (8). In patients with Alzheimer's disease, rhythmic methylation of BMAL1 has been found to be changed in the brains of patients with Alzheimer's disease, suggesting that alterations in the DNA methylation of clock genes may contribute to cognitive loss and behavior changes in individuals with Alzheimer's disease (9). Animal models of Parkinson's disease with 6-hydroxydopamine (6-OHDA) also show decreased BMAL1 and RORα that persisted with levodopa treatment, indication that long-term levodopa treatment may impair circadian rhythm function (10).

In regards to tumorigenesis and circadian rhythm involvement, TIMELESS, a mammalian homolog of a *Drosophila* circadian rhythm gene, has been found to be up-regulated in nasopharyngeal carcinoma and increased TIMELESS expression was associated with decreased overall survival. In addition, over-expression of TIMELESS led to resistance to cisplatin mediated apoptosis and activated the *wingless* pathway of Wnt/β-catenin pathway (11). Wnt proteins are cysteine-rich glycosylated proteins that oversee processes such as neuronal development, immunity, angiogenesis, fibrosis, stem cell proliferation, and tumorigenesis (12-14). Wnt and β-catenin signaling can block autophagy (15), apoptosis (16), affect sensory modalities (17), and lead to stem cell proliferation (18-20). However, these pathways can promote angiogenesis (21-23) and lead to tumor growth (24-29) that may align with the proliferative pathways of clock genes such as TIMELESS. On a clinical basis, disruption of circadian rhythms with shift work suggests that such duties also may increase the risk for developing cancer. Female nurses with long-term rotating night shift work had an increased risk for breast cancer (30). In addition, increased expression of the circadian gene *hClock* may contribute to tumorigenesis, such as the metastasis of colorectal cancer, through the enhanced expression of angiogenesis-related genes (31).

Circadian Rhythm and the Modulation of Autophagy

Autophagy is a process that recycles components of the cytoplasm in cells for tissue remodeling and eliminates non-functional organelles (32-36). The term macroautophagy refers to a classification of autophagy that recycles organelles and consists of the sequestration of cytoplasmic proteins and organelles into autophagosomes. These autophagosomes then combine with lysosomes for degradation and recycling (37, 38). Microautophagy describes the invagination of the lysosomal membranes for the sequestration and digestion of cytoplasmic components (39). Chaperone-mediated autophagy (40) uses cytosolic chaperones to transport cytoplasmic components across lysosomal membranes (41).

Autophagy can be involved in a number of degenerative disorders such as Alzheimer's disease (42-46), Parkinson's disease (41, 47, 48), Huntington's disease (49-51), and diabetes mellitus (12, 18, 33, 43, 52, 53). Importantly, autophagy also can impact cognitive decline (12, 54, 55) and aging processes (43, 56-60).

Interestingly, circadian rhythm dysfunction during cognitive loss and aging has been tied to the induction of autophagy (61). Studies with *Drosophila* show that the accumulation of neural aggregates observed with aging is associated with a reduction in the autophagy pathway. These neural aggregates lead to behavior impairments that can be resolved with the maintenance of autophagy pathways in neurons (62). In animal models of Alzheimer's disease, a basal circadian rhythm that controls macroautophagy may be necessary to limit cognitive decline and amyloid deposition (63). Even mild changes in the external environment that affect circadian rhythm may alter cognition. Chronic sleep fragmentation has been shown to affect autophagy proteins in the hippocampus (64) that may affect memory and cognition (44, 46, 55, 56, 65). In addition, autophagy in the hippocampus is depressed during the absence of the PER1 circadian clock protein that may worsen the pathology of cerebral ischemia (66).

Circadian Rhythm, mTOR and SIRT1

The potential of the mammalian circadian rhythm to control cell survival not only relies upon autophagy activity, but also upon other cellular signaling pathways that include the mechanistic target of rapamycin (mTOR) and the silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1). mTOR, also known as the mammalian target of rapamycin and the FK506-binding protein 12-rapamycin complex-associated protein 1 (44), is a 289-kDa serine/threonine protein involved in multiple cellular processes that include autophagy. mTOR is the principal component of the protein complexes mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2) (42, 44, 67, 68). mTORC1 contains the components 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/GβL) (27). mTORC2 contains Rictor, Deptor, mLST8, the mammalian stress-activated protein kinase interacting protein (mSIN1), and the protein observed with Rictor-1 (Protor-1) (17, 42).

mTOR can oversee multiple physiologic and disease processes such as cellular metabolism (69, 70), bone formation (71-73), diabetes (35, 43, 74-77), neurodegenerative disorders (37, 78-83), dementia (12, 84-86), and cancer (25, 27, 87-91). In addition, mTOR has a significant role in the modulation of autophagy induction (92). Important in the signaling cascade of mTOR is AMP activated protein kinase (AMPK). AMPK can prevent mTORC1 activity through the activation of the hamartin (tuberous sclerosis 1)/tuberin (tuberous sclerosis 2) (TSC1/TSC2) complex and can lead to the induction of autophagy (46, 58, 93-95).

In light of the close association between autophagy and mTOR, it may come as no surprise that circadian pathways are intimately linked to mTOR pathways. Melatonin, a pineal hormone that controls circadian rhythm, also relies upon autophagy pathways and mTOR to control processes of aging and neurodegeneration (3). Loss of mTOR activation may be involved with altered circadian rhythm and cognitive decline during prolonged space flight (96). Cerebral ischemic infarction also may be influenced by alteration in circadian rhythm genes and fluctuations in mTOR activity (66, 97). In regards to cancer, some studies suggest that loss of mammalian circadian clock proteins such as period2 (Per2) can lead to enhanced mTOR activity and chemotherapy drug resistance (98).

Pathways of mTOR and AMPK are also linked to SIRT1 (12, 99, 100). SIRT1, a member of the sirtuin family, is a histone deacetylase (51, 55, 101-106). SIRT1 can transfer acetyl groups from ε-N-acetyl lysine amino acids on the histones of DNA to control transcription and is dependent upon nicotinamide adenine dinucleotide (NAD^+) as a substrate (105, 107-110). Nicotinamide phosphoribosyltransferase (NAMPT) catalyzes the conversion of nicotinamide to nicotinamide mononucleotide through the salvage pathway of NAD^+ synthesis (70, 73, 108). Nicotinamide mononucleotide is subsequently converted to NAD^+ by enzymes in the nicotinamide/nicotinic acid mononucleotide adenylyltransferase (NMNAT) family.

SIRT1 is involved in multiple disease processes that include cancer (106, 111-113), vascular disease (39, 114-117), altered cellular metabolism (12, 102, 103, 118, 119), diabetes (18, 120-123), and neurodegenerative disorders (106, 124, 125). Many of these processes require the modulation of autophagy by SIRT1 (12, 40, 126, 127). SIRT1 controls stem cell survival by modulating autophagic flux (128) and SIRT1 activity is increased in conjunction with AMPK to lead to autophagy and cellular protection (129). Importantly, SIRT1 can have an inverse relationship with mTOR in embryonic stem cells (58, 70) and block mTOR to promote autophagy and protect embryonic stem cells during oxidative stress (130).

In regards to the control of circadian rhythm, SIRT1 may be involved with altered circadian rhythm function that affects the development of disorders such as Alzheimer's disease (131). Increased SIRT1 activity with a disruption in circadian rhythm also may result in increased susceptibility to mammary carcinogenesis (132). Yet, SIRT1 may be beneficial under specific circumstances to regulate circadian rhythm gene expression that can foster hepatocellular proliferation and liver regeneration following liver resection (133).

Conclusions and Future Perspectives

Located in the SCN, the mammalian circadian clock is emerging as a critical component for several disease processes that include aging related disorders, neurodegenerative diseases, and cancer. Relying upon cellular signals and light input to align itself with solar time, the circadian clock rhythm controls behavior, normal physiology, and biochemical cellular signal transduction. Neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease may progress in the setting of altered circadian rhythm dysfunction. In a similar manner, loss of a proper circadian rhythm may lead to increased risk for nasopharyngeal carcinoma, breast cancer, and metastatic colorectal cancer. Clinical behavior disruptions that involve prolonged shift work and even space travel may negatively impact circadian rhythm. At the cellular level, regulation of the pathways of autophagy, mTOR, AMPK, and SIRT1 as well as proliferative mechanisms that involve Wnt may be vital for the normal physiologic regulation of the body's circadian rhythm. As our knowledge continues to expand in regards to the significant role circadian clock genes hold for disease states, future targeting of the underlying pathways that control mammalian circadian rhythm may hold the key for the development of novel therapies against aging-related disorders, neurodegenerative disease, and tumorigenesis.

Acknowledgments

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

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