Sirtuin-dependent clock control: new advances in metabolism, aging and cancer

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Purpose of review
The circadian clock is an intricate biological timekeeper that is subject to fine-tuning mechanisms in order to maintain synchrony with the surrounding environment. One such mechanism is performed by the mammalian sirtuins that provide plasticity to the circadian clock by sensing cellular metabolic state. The sirtuins modulate the circadian epigenome and subsequent transcriptional control, and alterations to this organized system manifest in metabolic consequences, aging phenotypes and possibly cancer.

Recent findings
New information regarding sirtuin-dependent control of the circadian clock has emerged. In addition to sirtuin (SIRT)1 and SIRT3, SIRT6 has been demonstrated as a critical regulator of circadian transcription that also serves as an interface with metabolic homeostasis. Also, new metabolic functions of SIRT1 have been described in the brain, which are critical to relay nutritional inputs to the central clock.

Summary
This review focuses on the link between the circadian clock and the sirtuins, with an emphasis on new findings. In addition, speculation on the possible connections at the physiological level will be made that could further link the clock to aging and cancer.

Keywords
aging, cancer, circadian clock, metabolism, nutrition, sirtuins

INTRODUCTION

The circadian clock is a self-sustained biological pacemaker that operates with a periodicity of 24 h, the purpose of which is to synchronize and maintain homeostasis of a number of physiological processes [1,2]. Disruption in proper circadian timekeeping manifest in detrimental systemic effects and a number of clues from the clinic and laboratory suggest that these disturbances result in metabolic disruptions [3▪▪,4], cancer [5,6] and aging-related phenotypes [7–9]. At the heart of the circadian molecular machinery are the core DNA-binding transcription factors, CLOCK and BMAL1, which drive the oscillation of ~10% of transcripts in the genome in a defined tissue-specific programme [10,11]. CLOCK:BMAL1-dependent transcription of clock-controlled genes (CCGs) peaks during the day, while transcriptional feedback inhibition by the circadian repressors, period and cryptochrome, occurs at night [12,13]. In addition to the core transcriptional/translational feedback loop, regulation of circadian transcription is also subject to epigenetic modifications that are rhythmic over the day/night cycle [12,14]. An example of such histone modifications is mediated by the histone methyltransferases mixed lineage leukemia (MLL)1 [15] and MLL3 [16] on H3K4 that permit circadian gene expression, and intriguingly the trimethylation of H3K4 is regulated by sirtuin (SIRT)1 through cyclic deacetylation of MLL1 [17].

The mammalian sirtuins modulate the circadian epigenome and provide specificity in transcriptional control. The sirtuins are a nicotinamide adenine dinucleotide (NAD^+)-dependent family of histone deacetylases (HDACs), which are implicated in various physiological functions ranging from aging, maintenance of genome integrity, stress response to nutrient challenge, metabolic control and cancer [18–20]. Remarkably, the seven mammalian sirtuins vary in their enzymatic activity (aside from their

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KEY POINTS

- The sirtuins serve as a fine-tuning mechanism for regulating circadian transcription and providing plasticity which is dependent on cellular metabolic state.
- The sirtuins and the clock, therefore, coordinate a critical cross-talk between epigenetics, transcription and metabolism.
- Deregulation of the sirtuin/clock axis could result in detrimental effects such as cancer and aging-related phenotypes.

deacetylase function) [21], biological targets and cellular function [8,22]. The subcellular localization of the sirtuins is also varied: SIRT1 shuttles between the nucleus and cytoplasm, SIRT2 is cytoplasmic, SIRT3, SIRT4 and SIRT5 are mitochondrial, SIRT6 is nuclear and chromatin-bound and SIRT7 is found largely in the nucleolus [19,23].

UNSUSPECTED FUNCTIONS OF THE SIRTUINS IN REGULATING THE CLOCK

The mammalian sirtuins have been reported to regulate both the circadian clock in the brain and peripheral clocks, such as the liver (Fig. 1). Work from a number of laboratories has shown that SIRT1 is involved in regulating circadian epigenetic control through H3K9 deacetylation, modulation of BMAL1 and PER2 acetylation state and stability, and subsequent control of circadian gene expression [24,25]. Additionally, the circadian clock was previously shown to regulate mitochondrial oxygen consumption rate in an NAD^+/SIRT3-dependent manner [26]. Given that levels of NAD^+ are clock-controlled and oscillate over the circadian cycle [27,28], the question arises as to what other NAD^+-dependent sirtuins are involved in clock regulation.

Transcriptional control of SIRT6

In addition to the described roles of SIRT1 and SIRT3, SIRT6 was recently demonstrated to regulate the hepatic circadian clock. The defining feature of SIRT6 that distinguishes it from the other sirtuins is its constitutive chromatin localization [29,30], which is maintained over the circadian cycle [31▪]. SIRT6 deacetylates H3K9 [32,33] and H3K56 [34–36] which consequentially results in modulation of gene expression and telomere maintenance [37,38]. Strikingly, the genome-wide localization of SIRT6 is enriched at transcriptional start sites of active genomic loci, which are also occupied by serine 5 phosphorylated RNA polymerase II [39]. Collectively, these data suggest that SIRT6 functions as a transcriptional 'marker' that demarcates areas of the genome that are dynamically transcribed and subsequently silenced. Similarly, recent evidence supports a role for SIRT6 as an epigenetic safeguard for controlling proper cellular differentiation [40], suggesting that the HDAC function of SIRT6 is a critical control mechanism for proper transcription in multiple biological contexts. In further support of this concept, not only do SIRT6 and SIRT1 regulate unique sets of circadian genes in the liver, but SIRT6 is also involved in modulating the proper chromatin recruitment of CLOCK:BMAL1 and SREBP1 and thereby regulating circadian gene expression [31▪]. This partitioned control of the nuclear sirtuins also results in differential jurisdiction of SIRT6 and SIRT1 in regulating circadian fatty acid metabolism, carbohydrates, peptides and cofactors in the liver [31▪]. The SIRT6-dependent regulation of circadian fatty acid synthesis, beta-oxidation and storage as triglycerides is also intriguing given that free fatty acids are potent activators of SIRT6 HDAC activity *in vitro* [41], suggesting that a complex feedback regulation exists. These concepts underscore the unique ability of SIRT6 to dynamically modulate transcription in multiple contexts, one of which is the regulation of circadian gene expression in the liver.

Metabolic functions of SIRT1

Moreover, the complexity of sirtuin biology in regulating the clock is continually expanding as new roles for SIRT1 have recently emerged that dictate metabolic state. SIRT1 deacetylates and therefore modulates the circadian enzymatic activity of Acetyl-CoA Synthetase 1, an enzyme involved in the production of acetyl-CoA from acetate. This results in the oscillation of acetyl-CoA over the circadian cycle and subsequently controls fatty acid elongation [42▪▪]. Because acetyl-coA is a key carbon donor in metabolism, this establishes the possibility of other biological processes that are dependent on acetyl-CoA that could be linked to the clock and SIRT1. Also, the importance of nontranscriptional, metabolic and enzymatic feedback loops in circadian control [43], which are accompanying mechanisms to the classic transcriptional/translational pathways, is critical in clock biological output.

Along a similar metabolic premise, SIRT1 was shown to play an important role in translating nutritional cues in the brain. In the ventromedial hypothalamus (VMH), SIRT1 was found to control circadian rodent behavior under specific conditions of light and food restriction, which also extends to

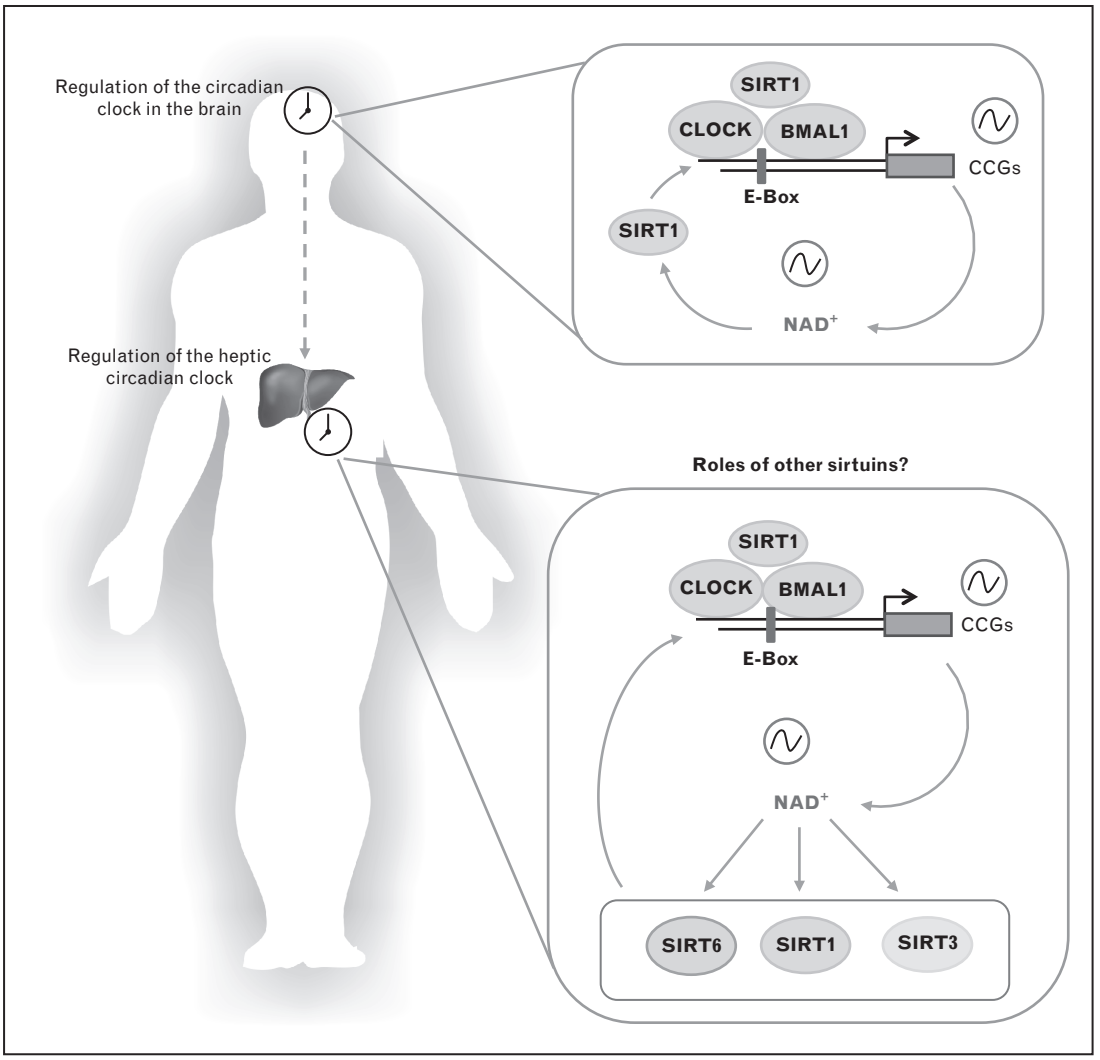

FIGURE 1. Sirtuin-dependent control of the circadian clock in the brain and periphery. The core clock transcriptional machinery, directed by CLOCK and BMAL1, drives transcription of circadian gene expression, including nicotinamide phosphoribosyltransferase (*Nampt*), which subsequently results in oscillatory levels of NAD^+. In the brain, NAD^+-dependent SIRT1 activity is critical for circadian function both in the SCN and VMH. In the liver, SIRT1, SIRT6 and SIRT3 are involved in circadian transcription and metabolic regulation. CCGs, clock-controlled genes; SCN, suprachiasmatic nucleus; VMH, ventromedial hypothalamus.

effect circadian gene expression of the central clock in the suprachiasmatic nucleus (SCN) [44▪]. These results show that SIRT1 is a nutritional sensor in the VMH and is able to transmit metabolic information to the central clock that dictates systemic circadian behavior and rhythms. These data further demonstrate the plasticity of the clock system, which is adaptive to its environment, and the importance of SIRT1 as a sensor that can transmit nutritional cues to alter transcriptional profiles.

The circadian clock has previously been implicated in insulin signaling. Insulin levels are dynamically rhythmic, and genetic mutant models of the clock in rodents demonstrate the circadian effects on insulin and hepatic glucose production [45–48]. Similarly, SIRT1 has been reported to be involved in pancreatic beta cell secretion of insulin [49] as well as a key regulator of insulin sensitivity [50]. The first preliminary data on circadian regulation of insulin sensitivity that is linked to SIRT1 were recently demonstrated in cultured hepatocytes, whereby insulin resistance induced by circadian misalignment was attenuated by pharmacological induction of SIRT1 activity [51]. These preliminary data are tantalizing, though require further mechanistic insights *in vivo* to determine how critical SIRT1, or any other sirtuin, is to the insulin pathway.

CIRCADIAN CLOCK, SIRTUINS AND CANCER

In humans, circadian disruption which is prominent in shift workers puts them at increased risk

for breast cancer [52]. In mice, an ablation of the central clock located in the SCN results in increased growth of tumor xenografts as compared with mice with an intact circadian pacemaker [53]. Also, the *Per2*$^{m/m}$ mice are highly sensitive to γ-irradiation and exhibit increased levels of salivary gland hyperplasia [54]. The tumor suppressor p53 regulates *Per2* expression by blocking CLOCK:BMAL1-dependent recruitment to the *Per2* promoter and strikingly, p53-null mice exhibit a shorter circadian period and impaired photo-entrainment [55]. Most recently, the cancer/testis antigen PAS domain containing protein 1 (PASD1), the expression of which is induced upon oncogenic transformation, was shown to interact with the clock complex and thereby repress circadian transcription [56]. Knockdown of PASD1 in human cancer cells was able to rescue the amplitude of circadian expression [56], though what remains to be determined is the effect of PASD1 knockdown on tumorigenesis *in vivo*. Remarkably, these results indicate that loss of functional circadian transcription may be a mechanism by which oncogenic transformation or tumor progression can occur. Yet, these results require additional experiments to determine the extent and molecular mechanisms by which the circadian clock is linked to cancer.

The connection between the circadian clock, the sirtuins and cancer has not been well established, yet a number of possible links can be made and will be discussed here. It is clear that SIRT1 does play a role in cancer, though this function seems to be context specific as SIRT1 has been reported to be a tumor suppressor and promoter. These ideas have been recently reviewed [57,58], and therefore we only focus on new data regarding the role of SIRT1 and cancer. Recent evidence elegantly illustrates that SIRT1 expression is elevated in leukemic stem cells, and a cross-talk exists between SIRT1 and v-myc avian myelocytomatosis viral oncogene homolog (MYC) oncogenic signaling that is responsible for driving FLT3 receptor tyrosine kinase resistance in acute myeloid leukemia [59]. These data are interesting from a circadian perspective for two reasons. First, MYC is an E-Box binding transcription factor, similar to CLOCK and BMAL1, and the extent to which these two transcriptional programs overlap and share common gene targets is unknown. Therefore, SIRT1 could be playing a role in modulating more than one E-Box-driven transcriptional pathway. Second, the role of the circadian clock, SIRT1 and MLL has been described [15,17], and it is likely that this transcriptional circuit could be highly relevant to leukemia. Indeed, recent evidence provides a mechanistic checks and balances system between the SIRT1 repressive chromatin complex and the MLL/DOT1L histone methyltransferase complex that is aberrantly expressed in some forms of leukemia. The DOT1L histone methyltransferase (required for H3K79 dimethylation) cooperates with the MLL complex to aberrantly express a number of genes that drive tumorigenesis in leukemia driven by MLL rearrangement. This MLL-dependent transcription is counterbalanced by SIRT1 repressive deacetylation of H3K9 and subsequent methylation by SUV39H1 to restore gene expression profiles [60]. These results provide exciting new avenues for the need for pharmacological SIRT1-based intervention in MLL-rearranged leukemia.

Moreover, in human pancreatic ductal adenocarcinoma tumor specimens and matched normal pancreatic tissue, a marked deregulation of *Sirt1* and a number of circadian genes (*Bmal1, Per1–3* and *Cry1–2*) were observed, and an interesting correlation was seen whereby the expression of these genes was altered upon serum starvation in pancreatic cancer cell lines [61]. These data point to a nutritional sensing mechanism whereby SIRT1 activity can be altered, which may have beneficial therapeutic effects.

SIRT6 has long been described as a key regulator of genome stability [29,36], and this concept agrees with data suggesting the role of SIRT6 as a tumor suppressor. SIRT6 is a potent regulator of aerobic glycolysis in cancer cells, which is a key mechanism for energy production upon which cancer cells are reliant on for growth [62]. Loss of SIRT6 alone, without the activation of known oncogenes, results in tumor formation suggesting that this metabolic switch results in tumor initiation and most likely also drives tumor progression [62]. Although the direct link between SIRT6, cancer and the circadian clock has not been made, the SIRT6-dependent metabolic control mechanisms involved in oncogenic transformation are a tempting connection to the metabolic control exerted by the circadian clock. Indeed, a number of recent reports also show an association between metabolic state dictated by SIRT6 and different cancer types [63–65].

CIRCADIAN CLOCK, SIRTUINS AND AGING-RELATED DISEASES

The role of SIRT1 in regulating the central circadian clock in the SCN has been linked to aging and recent reviews have covered this topic in detail [66,67]. The brain-specific *Sirt1*$^{-/-}$ [brain-specific SIRT1 knockout (BSKO)] mice exhibit dampened circadian gene expression in the anterior hypothalamus (where the SCN is located), suggesting that SIRT1 positively regulates clock-controlled transcription [68]. These

changes in gene expression result in altered circadian function, as the BSKO mice exhibit a lengthened circadian period and remarkably, at 5 months of age, the BSKO mice phenocopy the 'aged' phenotype observed in 22-month-old wildtype animals [68]. These data suggest that loss of SIRT1 in the brain not only regulates the circadian clock but also accelerates the aging process, which is most likely mediated by NAD^+. Changes in mitochondrial oxidative phosphorylation state were reported in aging and this was attributed to a decline in nuclear NAD^+ levels and dependent on SIRT1 enzymatic activity [69]. Given that the circadian clock regulates oscillatory levels of NAD^+ [27,28], and that circadian transcription is dampened in the aging brain [68], the decline in NAD^+ levels during aging could be attributed to loss of clock function. Recent therapeutic strategies have been described using caloric restriction that could rescue the aging phenotype in cardiomyocytes [70] and adipose tissue in an SIRT1-dependent manner [71].

To date, the role of SIRT6 and aging has not been linked to the clock, but a number of clues suggest that a probable connection exists. Genetic mouse models revealed that SIRT6 is involved in aging because of a number of reported factors: SIRT6 is implicated in regulation of genome stability [29], DNA repair [72,73], telomere maintenance [33,34], and the dynamic regulation of stress and aging responsive genes [32,74,75]. Given the aging-dependent decline in NAD^+ levels [69] (that could be related to the loss of circadian function), it may be possible that SIRT6 activity would, therefore, decline with age and have many deleterious effects. For example, DNA repair has been linked to the circadian clock [76–78] and to SIRT6 [72,73], and whether this connection is related to aging is currently unknown. Also, male SIRT6 transgenic mice exhibit an extension in lifespan because of possible changes in the insulin-like growth factor 1 (IGF-1) signaling axis [75]. Interestingly, growth hormone, which stimulates the production of IGF-1, is known to oscillate in a sleep and clock-dependent manner [79], raising the possibility that the aging phenotype in SIRT6 transgenic animals could have a circadian connection. These possible connections between SIRT6, and even other mammalian sirtuins, in the context of clock control and aging require further exploration.

CONCLUSION

The circadian clock is a tightly regulated system that is essential to maintain organismal homeostasis in behavioral, metabolic and endocrine rhythms. Yet, circadian timekeeping is subject to numerous environmental cues that are needed to adjust our internal biological pacemaker to the environment, cellular metabolic state and even stress response. Therefore, the need for 'metabolic sensors' to modulate circadian rhythms is a necessity, and one class of these sensors is the mammalian sirtuins. To date, SIRT1, SIRT3 and now SIRT6 have been implicated in circadian control, both in regulating the central clock in the SCN and peripheral clocks. The accumulating data on the sirtuins demonstrate that these HDACs are critical in the cross-talk between epigenetics, transcription and metabolism. Our understanding of the extent to which the sirtuins regulate the clock is still incomplete, and possibly other SIRTs are also implicated in circadian control in the cytoplasm and nucleolus. Also, this review explores the possible connections linked to aging and cancer, yet we await more experimental evidence that will clarify the functions of the sirtuins in homeostatic control and contexts of disease state.

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Conflicts of interest

There are no conflicts of interest.

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