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Circadian clock: linking epigenetics to aging

Ricardo Orozco-Solis and **Paolo Sassone-Corsi**

Center for Epigenetics and Metabolism, Department of Biological Chemistry, University of California, Irvine, Irvine, CA 92697, United States

Abstract

Circadian rhythms are generated by an intrinsic cellular mechanism that controls a large array of physiological and metabolic processes. There is erosion in the robustness of circadian rhythms during aging, and disruption of the clock by genetic ablation of specific genes is associated with aging-related features. Importantly, environmental conditions are thought to modulate the aging process. For example, caloric restriction is a very strong environmental effector capable of delaying aging. Intracellular pathways implicating nutrient sensors, such as SIRTs and mTOR complexes, impinge on cellular and epigenetic mechanisms that control the aging process. Strikingly, accumulating evidences indicate that these pathways are involved in both the modulation of the aging process and the control of the clock. Hence, innovative therapeutic strategies focused at controlling the circadian clock and the nutrient sensing pathways might beneficially influence the negative effects of aging.

Introduction

Along evolution, all life forms have adapted to a 24 hours day–night cycle and anticipate circadian (from Latin *circa diem*, approximately a day) fluctuations in the environment. The central clock is localized in the suprachiasmatic nucleus (SCN) of the hypothalamus that is daily synchronized by the light stimulus through the retinohypothalamic tract (RTH). Moreover, non-photic stimulus such as nutritional inputs involving feeding time and diet composition can also entrain the clock [1,2,3•,4]. In addition to the SCN, peripheral clocks are localized in other brain areas, including nuclei within the hypothalamus and the hippocampus, as well as in peripheral tissues including the liver, kidney, heart, among others. These are synchronized in concert with the central clock, but are also influenced by additional stimuli, including food, hormones, among others. At the molecular level the clock consists of a network of interlocked transcriptional-translational feedback loops. The core molecular gears of this machinery are the transcription factors Circadian Locomotor Output Cycles Kaput (CLOCK) and Brain and Muscle ARNT-Like 1 (BMAL1), which heterodimerize and bind E-box promoter elements on the genome, activating a large number of clock-controlled genes (CCGs). Within the CCGs, the Period 1-3 (*Per1, Per2* and *Per3*) and Cryptochrome 1-2 (*Cry1* and *Cry2*) genes encode clock proteins that associate together and repress CLOCK–BMAL1, inhibiting their own expression by a negative autoregulatory feedback loop.

Corresponding author: Sassone-Corsi, Paolo (psc@uci.edu).

A number of CCGs encode for transcription factors, including D-box binding protein (DBP), thyrotroph embryonic factor (TEF), retinoic acid-related orphan receptor a (RORα) and reverse erythroblastosis virus α and β (REV-ERBα/β). DBP and TEF bind D-boxes, while RORα and REV-ERBα/β bind Reb-Erb/ROR promoter elements, thereby inducing additional circadian waves in expression of downstream genes. It is estimated that the circadian machinery controls the cyclic expression of about 10–20% of genes in any given cell [5], although recent findings indicate that many more genes may become circadian depending on nutritional and metabolic inputs [6••]. Importantly, epigenetic control appears to play a central role in the harmonic organization of circadian transcription [5,7,8,9••]. The circadian clock participates in homeostatic control by governing a number of physiological processes, metabolism, behavior, endocrine regulation, and cellular pathways. Hence disturbances in the circadian clock have been associated to various pathologies including, obesity, type-2 diabetes, feeding disorders, sleep disorders, Alzheimer's disease and psychiatric disorders.

The circadian clock in aging

It is common knowledge that elderly individuals have difficulties of sleeping at night, and they wake up at early morning [10]. Indeed, disruption of the circadian clock has been associated with several age-related pathologies including sleep disorders, diabetes, cancer, and memory reduction [10]. For example, daily fluctuations in the levels of hormones (including melatonin and cortisol), body temperature, and the sleep-wakefulness cycle are modified during aging. These changes lead to disrupted cycles, including reduction in the amplitude and phase shifts [11]. Moreover, in an intriguing experiment, cultured fibroblast expressing a luciferase reporter under the control of *Bmal1* promoter was treated with serum from young and old individuals. This resulted in shortening of the circadian period and phase advance in the cells, as measured by luminescence, suggesting that a circulating factor present in the serum of older individuals is altering the cellular rhythms. Interestingly, the serum factor from old people is not melatonin non-cortisol, since there were no differences in the levels of these hormones from young and older blood donors [12].

The notion that the circadian clock might modulate the rate of aging is further supported by early studies made in rodents showing that the graft of fetal SCN to a model of aged hamsters (known as $tau^{s/+}$) restores behavioral rhythmicity and extends the life span [13]. In line with this observation, the transplantation of pineal gland, from young to old mice, prolongs life span [14]. In this context, the hormone melatonin produced in the pineal gland is a strong synchronizer. The synthesis and secretion of melatonin fluctuate with the day/night cycles, and are under the control of sympathetic innervation from the SCN [15–17]. Moreover, in addition to its chronobiological activities, melatonin also exhibits immunomodulatory, neuroendocrine and antioxidant activities; all of these contribute to its anti-aging properties [18]. Notably, the amplitude of plasmatic melatonin rhythms shows progressive reduction with aging. Additionally, melatonin operates as direct scavenger for free radicals and induces the expression and activity of antioxidant enzymes [19]. In this context, a functional relationship between anti-oxidative mechanisms and the circadian clock has been established. Several anti-oxidative enzyme activities and low molecular weight antioxidants follow circadian rhythms [19]. Moreover, experimental evidence shows that

reactive-oxygen species (ROS) also follow circadian fluctuations [19]. Hence, it has been suggested that the circadian clock regulates mechanisms to protect the organism from oxidative stress [20]. For example, recent observations reveal that the dimer CLOCK:BMAL1 regulates the expression of the transcription factor NRF2 in the lung, which in turn, drives the circadian transcription of antioxidant genes. Some of these include the glutamate-cysteine ligase modifier subunit (*Gclm*) and the glutathione S-transferase A3 (*Gsta3*). Hence, the clock machinery modulates the circadian anti-oxidant response in lungs [21]. Importantly, results obtained from transgenic animals have confirmed the interplay of the circadian clock and aging and have also provided useful mechanistic leads for exploration. Specifically, ablation of the *Bmal1* gene (define) by homologous recombination in the mouse results in accelerated aging and increased levels of ROS in several tissues [22]. Finally, additional evidence has revealed some of the mechanisms that are behind the age-related pathologies associated to circadian disruption. Specifically, as discussed below, cellular energy/nutrient sensing mechanisms seem to be critical in both circadian control and the aging process [23–25].

SIRT1: linking the clock with metabolism

The enzyme SIRT1, a NAD^+ dependent deacetylase, targets a large variety of proteins, both histones and non-histones, including FOXO1, PGC1α, p53, E2F1, PPARγ, STAT3 and SCREBP-1c [19,20] (define). The histone deacetylase (HDAC) activity of SIRT1 oscillates in a circadian manner, rhythmically deacetylating histone H3 K9/K14 at promoters of CCGs, and the circadian core proteins BMAL1 and PER2 (define) [7,8]. Additionally, genetic ablation of *Sirt1* or pharmacological inhibition of SIRT1 provokes disturbances in circadian cycles, both in cultured cells and *in vivo* [26,27]. It has been suggested that the activity of SIRT1 counterbalances the rhythmic histone acetyltransferase (HAT) function of CLOCK, although other HATs are likely to be implicated [28]. Importantly, it has been found that the activity of SIRT1 is modulated by in a circadian manner by its cofactor NAD^+ [8]. NAD^+ can be synthesized *de novo* from tryptophan or by the salvage pathway [29]. NAD^+ can be used for energy transferring with the subsequent production of ATP in the mitochondria, or it is used in regulatory functions as a cofactor for NAD^+-consuming enzymes. Remarkably, the circadian clock acts on the synthesis of NAD^+, controlling the circadian expression of the nicotinamide phosphoribosyltransferase (*Nampt*) gene, a CCG that encodes the key rate-limiting enzyme in the salvage pathway [26,30]. Thus, the circadian feedback transcriptional loop is tightly linked to an enzymatic feedback loop (Figure 1). Furthermore, the NAD^+/NADH ratio apparently changes with feeding in the hypothalamus and peripheral tissues such as the liver, possibly inducing cyclic activation of SIRT1 enzymatic activity [31,32]. Importantly, recent evidence has shown that the levels of NAD^+ decrease during aging, hence impacting SIRT1 activity [33••].

SIRT1: linking the clock with aging

The hypothalamus controls a wide array of physiological functions that are modulated by aging. For example, the hypothalamus controls the whole organism energy balance, and malfunctioning of this control can trigger aging-associated metabolic disturbances such as obesity and type-2 diabetes. The hypothalamus also controls the sleep/wakefulness cycle

that is altered in elderly individuals [10,34]. Importantly, the deciphering of the cellular mechanisms within these neuronal circuits has revealed the importance of nutrient-sensing pathways in the neuronal responses toward the body's energy balance and aging. Among these sensors, the role of SIRT1 has been analyzed in different hypothalamic nuclei. SIRT1 is necessary for the adaptation to fasting, and in conditions of caloric restriction, it triggers lipid mobilization from the adipose tissue, a switch from glucose to lipid oxidation in skeletal muscle and liver, and an increase in hepatic glucose production [34]. SIRT1 is necessary in neurons of the ventro-medial hypothalamus (VMH) and arcuate nucleus (ARC), to control glucose metabolism and lipid metabolism in peripheral tissues whose unbalance are hallmark of aging [34,35]. SIRT1 has been reported to protect against Alzheimer's disease, amyotrophic lateral sclerosis and axonal degeneration. Importantly, a recent study demonstrated that mice overexpressing SIRT1 in the brain, particularly in the hypothalamic nuclei dorsomedial hypothalamus (DMH) and lateral hypothalamus (LH) show increased lifespan, mitochondrial function in skeletal muscle and improved sleep quality [36•]. This ‘age-delayed’ phenotype is correlated with an increase of neuronal activity of the DMH and LH through an increment in the expression of the orexin type 2 receptor (Ox2r) [36•]. Importantly, in the SCN, SIRT1 modulates the central clock, in a process that appears to become less efficient in aged animals [37••]. This modulation comprises a direct deacetylation of BMAL1 by SIRT1 [32,38] through PGC-1α and NAMPT [37••] (define).

An additional aspect that links the circadian clock to the aging process is the control of energy metabolism in the mitochondria. Importantly, an unbiased analysis of the circadian acetylome has revealed that the large majority of clock-controlled acetylation relates to mitochondrial proteins [39•]. This his finding is in keeping with the involvement of SIRT3, a sirtuin that targets mitochondrial proteins, in clock control. SIRT3 appears to generate rhythms in the acetylation and activity of oxidative enzymes and respiration in the mitochondria of the liver [40••]. Some of these enzymes are discussed in McMurray in this issue. However, it is unclear whether this mechanism is influenced during aging. Nevertheless, SIRT3 regulates mitochondrial anti-oxidative stress in hematopoietic stem cells, being required to maintain mitochondrial homeostasis during oxidative stress or aging [41•]. Furthermore, it has been observed that in conditions of critical oxidative stress, cells respond by resetting the circadian clock, activating anti-oxidant pathways through BMAL1, heat shock factor 1 (HSF1) and casein kinase II (CK2) [42]. Interestingly, SIRT1 also participates in mitochondrial anti-aging function by modulating the nuclear-mitochondrial communication. It appears that the decrease in NAD^+ levels during aging affects SIRT1 activity and thereby the control of nuclear-coded mitochondrial-genes [33••]. Hence, the decreased levels in NAD^+ might impinge negatively on mitochondrial homeostasis by inhibiting the activity of sirtuins (Figure 2).

Nutrient sensing and feeding restriction: the clock-aging interaction

The concept that genetic components control aging derives from various observations, including that different species display different extents of longevity. Moreover, the manifest role played by environment on the aging process illustrates the presence of an epigenetic component [43]. In this context, caloric restriction (CR) is a powerful environmental intervention that delays the effects of aging in experimental models such as yeast, worms,

flies and mice [23,44]. Importantly, CR experimental protocols are generally accompanied by temporal feeding. Indeed, the nutrient/metabolic sensor system that acts on the generation of beneficial cellular adaptations during CR and consequently delaying aging, also modulates the central clock [37••, 45•] (Table 1). These notions support the concept that the circadian clock is positioned downstream of metabolic sensors, acting as an effector and thus controlling cellular and physiological homeostasis. For example, mice fed with high fat diet (HFD) only during the mice's activity period show less body weight and better glucose metabolism accompanied by more robust circadian rhythms, despite their consumption of the same quantity of calories than the *ad libitum* fed mice [3•]. Thus, the synchronization of the circadian clock by the environment appears critical for the correct control of cellular and body homeostasis. In this context, recent experimental data in humans have shown the association between short sleep duration and the development of metabolic unbalances [46–48].

mTOR: another defense against aging

The mammalian target of rapamycin, mTOR, has been involved in the control of aging and caloric restriction effects. mTOR is a kinase that integrates nutrients, stress, growth and energy status inputs with cellular metabolic resources to balance catabolic and anabolic pathways. mTOR is found in two multi-protein complexes named mTORC1 and mTORC2 [49]. Caloric restriction reduces mTORC1 activity, and pharmacological or genetic disruption of mTORC1 is sufficient to extend lifespan in invertebrates and mice under normal caloric conditions [44]. Interestingly, a role for mTOR in the circadian clock has been shown. In the SCN, mTOR shows circadian activity, and photic signals activate mTOR signaling, which in turn promotes the translation of *Vip* (vasoactive intestinal particle) mNA by repressing 4E-BP1 [45•]. Finally, the clock seems to modulate negatively the mTOR pathway by a mechanism that involves BMAL1 [25]. These data stress the intrinsic cooperation between the photic and non-photic stimuli (i.e. feeding restriction) to modulate the circadian clock through nutrient sensor pathways such as SIRT1, AMPK, and mTOR, which in turn could be modulated by the circadian clock, generating a loop that could be both beneficial or prejudicial for healthy aging, depending on environmental factors (Table 1 and Figure 3).

Concluding remarks

Despite the advances in medicine during the past century, a significant increment in the morbidity of noninfectious diseases such as cancer, type-2 diabetes, obesity and mental illness is evident. This trend has been associated to a diminution in the quality of life. Studies during the past years have permitted to identify key molecular mechanisms behind the aging process. In this respect, the remarkable role of cellular nutrient sensing pathways has allowed the development of strategies including genetic, diet protocols (such as the reduction in calories and/or the use of most appropriate meal schedules), and pharmacological approaches.

Furthermore, recent evidence shows a clear link between the circadian clock and nutrient sensors that ultimately may modulate anti-aging and homeostatic mechanisms. Hence,

therapeutic strategies that would include circadian regulation of metabolism and physiology are to be taken seriously into consideration [50]. Attempts to modulate these pathways through chronotherapy are likely to enhance their anti-aging properties and dampen possible side effects [23,51,52]. Finally, taking into consideration the notion of integrons in aging [53] and the observation that key tissues are able to influence the whole body homeostasis [36•, 41•, 54] (Figure 3), it is conceivable that monitoring the aging-rate in these key tissues would substantially improve the healthy aging in the whole organism.

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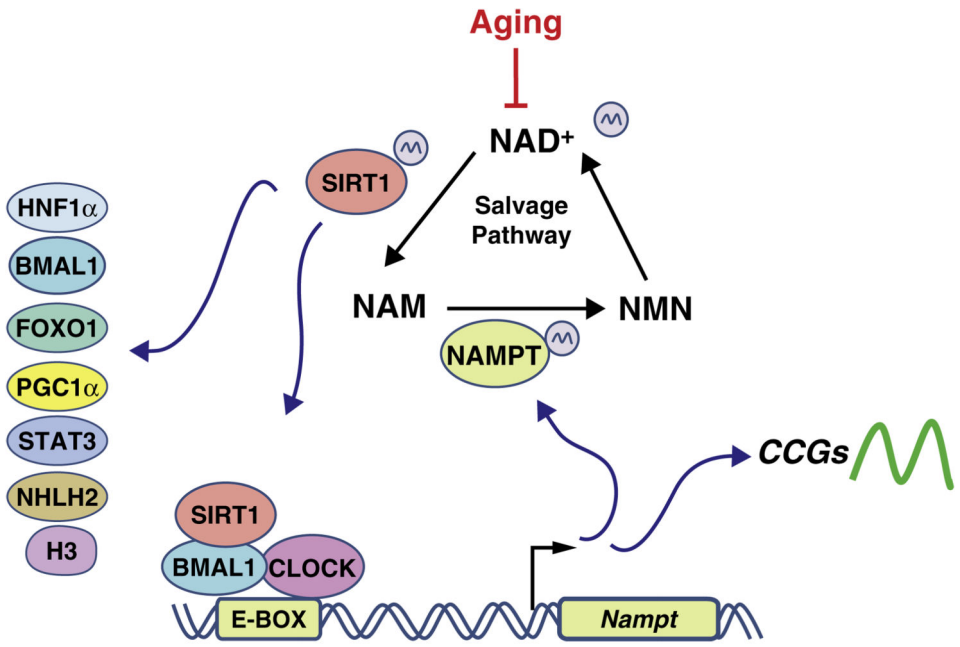

Figure 1.

The NAD^+ salvage pathway and its control by the circadian clock. The biosynthesis of NAD^+ follows a circadian pattern, which is caused by the circadian expression of NAMPT, a rate-limiting enzyme in the NAD^+ biosynthetic salvage pathway. The *Nampt* gene contains E-boxes in its promoter, leading to direct transcriptional control by the dimer CLOCK:BMAL1. The fluctuating levels of NAD^+ modulate the activity of SIRT1 which in turn regulates the transcriptional activity of CLOCK:BMAL1 on their targets genes. During the aging the levels of NAD^+ decreases and might alter the circadian rhythms of clock-controlled genes (CCGs)

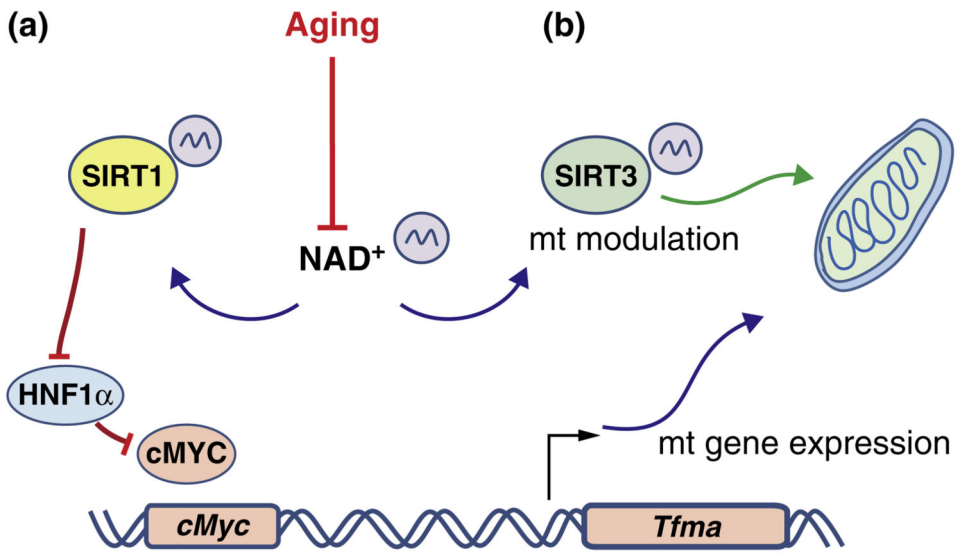

Figure 2.

Aging alters mitochondrial homeostasis. During aging the NAD^+ synthesis decreases and consequently impairs the sirtuins activity, which have two consequences in the mitochondrial function: **(a)** The reduction of SIRT1 activity provokes the activation of HNF1α which in turn inhibits the transcription factor cMYC necessary to activate the transcription of *Tfam* which regulates the expression of mitochondrial genes. **(b)** Reduction of SIRT3 activity alters the function of mitochondrial proteins.

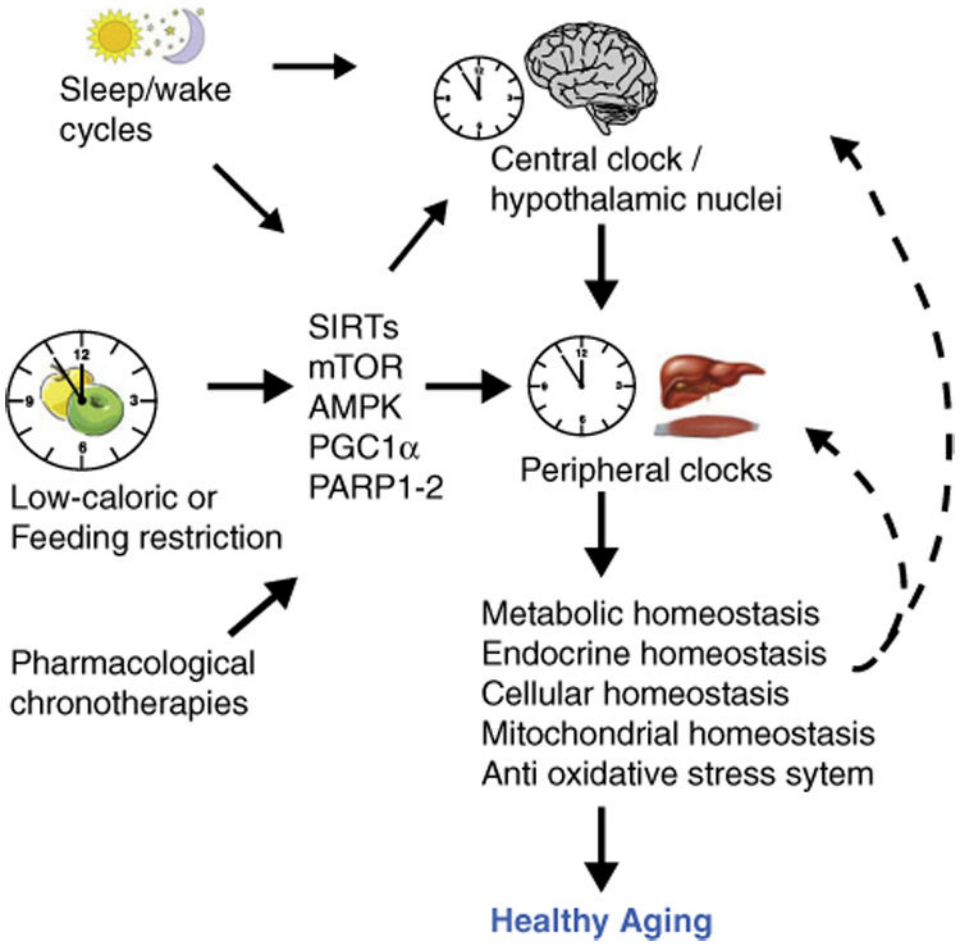

Figure 3.

Nutrient sensors ‘sense’ the environmental conditions that modulate the circadian clock and the aging process. Healthy environment, such as enough sleeping time and low caloric diet/scheduled feeding, modulates nutrient sensors localized in the brain and peripheral tissues. These in turn synchronize the circadian clocks. As a consequence, the activation of anti-aging mechanisms improves the homeostasis at different levels promoting healthy aging. The different physiological conditions might decelerate or accelerate aging.

Table 1

Nutrient sensors linking the clock system to the aging process

Protein	Circadian function	Aging phenotype	Reference
SIRT1	Regulates the circadian clock by BMAL1 and PER2 deacetylation. Activates BMAL1 and CLOCK in the SCN in young mice	Modulates mitochondrial function through NAD^+ levels in young mice	[7,8,33••,37••]
SIRT3	Modulates the circadian activity of the mitochondria by rhythms in the acetylation and activation of oxidative enzymes	In stems cells reverts the effect of aging-oxidative stress in mitochondria activating the anti-oxidative defense system	[40••,41•]
mTOR	Modulates rhythmically the translational control in circadian genes through 4E-BP1	Its inhibition extends lifespan in mice	[24,45•,49]
AMPK	Phosphorylates and destabilizes CRY1 altering the circadian rhythms in mice	Activated under low ATP levels, inhibits mTOR, and its pharmacological activation extend lifespan in mice	[52,55]