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More than Meets the Eye: Biological Clocks

Roberto Paganelli*

Department of Medicine and Sciences of Aging, University G d Annunzio and Ce. S.I. Me.T, Italy

***Corresponding author:** Roberto Paganelli, Department of Medicine and Sciences of Aging, University "G d'Annunzio" and Ce.S.I.-Me.T., Chieti, Italy

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Commentary

The discovery of an intrinsically photosensitive small subgroup of retinal ganglion cells which regulates the circadian rhythms on the light-dark cycle has stimulated the search for the molecular clock(s) driving this essential component of all living organisms. A handful of genes and proteins accounting for this complex regulatory network has been identified, and the Nobel Prize for Physiology or Medicine has been awarded in 2017 to three of the principal scientists who contributed to this research field ; (http://www.nobelprize.org/nobel_prizes/medicine/laureates/2017/press.html?utm_source=twitter&utm_medium=social&utm_campaign=twitter_tweet, accessed on Oct. 5th, 2017).

The mammalian networks consist of two feedback loops [1] connected by a central pair of transcription factors [2,3]; PER, the protein encoded by *period* [4,5] accumulates during the night and is degraded during the day, thus regulating circadian gene transcription by interacting with transcription factors [6]; other components drive the circadian oscillation and allow nuclear translocation of PER [7-10]. Both sleep-wake cycles and many 24-hour physiological rhythms persist in the absence of environmental cues; genetic and biochemical studies have shown that such rhythms are controlled by internal molecular clocks [11]. This mechanism involves neural control and the central pacemaker in the supra chiasmatic nucleus of the hypothalamus, which synchronizes circadian oscillators in periphery.

The core mechanism consists of three genes: period (per), timeless (time), and double time (dbt). Heterodimerization of PER and TIM proteins allows nuclear localization and suppression of further RNA synthesis by a PER/TIM complex [12]. Light resets these molecular cycles by eliminating TIM. Transcriptional feedback loops are central to the generation and maintenance of circadian rhythms [13]. The mammalian circadian clock fundamentally depends on two master genes CLOCK and BMAL1 to drive gene expression and regulate biological functions in a circadian rhythm; CLOCK: BMAL1 DNA binding promotes rhythmic chromatin opening and this mediates the binding of other transcription factors adjacent to CLOCK: BMAL1 [14].

Circadian photo entrainment is the process by which the internal clock in the deep brain becomes synchronized with the daily external cycle of solar light and dark. In mammals, this process is mediated by a class of retinal ganglion cells that send axonal projections to the supra chiasmatic nuclei, the region of the circadian pacemaker. In contrast to retinal cells mediating vision, these cells are intrinsically sensitive to light, independent of synaptic input from rod and cone photoreceptors [15]. The circadian system is organized in a hierarchical manner, with the central pacemaker in the supra chiasmatic nucleus which synchronizes oscillators in peripheral tissues. Photo entrainment of the master pacemaker needs signaling from retinal ganglion cells containing the photo pigment melanopsin and intrinsically photosensitive [16]. Cryptochromes Cry1 and Cry2 are integral components of the circadian pacemaker in the brain and contribute to circadian photoreception in the retina [17]. The cryptochrome/photolyase family of photoreceptors mediates adaptive responses to ultraviolet and blue light exposure in all life forms [18].

The central biological CLOCK system, influenced by light/dark changes, 'creates' the internal circadian rhythms, and the organism 'feels' these changes to put in frame physical activities, including energy metabolism, sleep, and immune function. A wide range of immune parameters, such as the number of peripheral blood mononuclear cells as well as the level of cytokines, undergo daily fluctuations.

Many immunological functions depend on the influence of sleep on circadian rhythms, and loss of sleep, in turn, alters the production of glucocorticoids during the night [19]. The neuroendocrine immune response of the hypothalamic-pituitary adrenal (HPA) axis and sympathetic nervous system, which is activated in response to an antigenic challenge, implying a transient inflammatory activity, can lead to metabolic diseases onset when chronically activated [20], since in all inflammatory conditions high amounts of energy have to be provided for the activated immune system. Experimental animal models and epidemiological data indicate that chronic circadian rhythm disruption increases the risk of metabolic diseases [21].

In patients with rheumatoid arthritis (RA), inflammation is an important covariate for the crosstalk of sleep and the HPA axis. Moreover the interrelation between sleep parameters and

inflammation is objectified by C-reactive protein and serum cortisol and adrenocorticotropic hormone levels [22]. Knowledge of circadian rhythms and the influence of glucocorticoids in rheumatology is important [23]: beside optimizing treatment for the core symptoms (e.g. morning stiffness in RA), chronotherapy might also relieve important comorbid conditions such as depression and sleep disturbances [24]. Sleep and circadian disturbances are a frequent complaint of Alzheimer's disease patients, appearing early in the course of disease, and disruption of many circadian rhythms are present also in Parkinson's disease [25].

Physiological studies show that aging affects both sleep quality and quantity in humans, and sleep complaints increase with age [26]. More, also feeding/fasting rhythms are compromised. Circadian expression of secreted signaling molecules transmits timing information between cells and tissues. Such daily rhythms optimize energy use and temporally segregate incompatible processes. Patients suffering from neuropsychiatric disorders often exhibit a loss of regulation of their biological rhythms which leads to alterations of sleep/wake, feeding, body temperature and hormonal rhythms. Increasing evidence indicates that the circadian system may be directly involved in the etiology of these disorders [27].

Light, especially short-wavelength blue light, is the most potent environmental cue in circadian photo entrainment and lens aging is thought to influence this event by acting as a filter for shorter blue wavelengths [28]; light conditions during indoor activities as well as sunlight exposure are of paramount importance to preserve the circadian rhythmicity and avoid a risk factor for several chronic diseases. These considerations impact on the comorbidities of aged subjects and the importance of the choice of the differential light-filtering properties of intraocular lenses after cataract removal [29]. As an important addendum to the many health consequences of abnormalities of the integrated circadian rhythms, one must just mention disorders in glucose and lipid metabolism as inducers of obesity and the development of Type 2 diabetes [30] and the multifaceted effects of the circadian control of the immune system and its activation [31,32]. These findings highlight an integrative role of circadian rhythms in physiology [33].

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