INVITED EDITORIAL

Genetics of circadian rhythm in disease and aging process

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There are multiple peripheral clocks located in various tissues and organs of the body, which cause variations in biological activities and are involved in the generation of circadian rhythms. In mammals, the circadian rhythm is generated by an endogenous timing system known as the circadian clock, which is 24 hours long. During each day, the circadian clock coordinates with environmental cues to regulate many cellular, behavioral, and physiological processes. During the day, a rise in heart rate, blood pressure, temperature and body activity is observed, while in the evening there is a decrease in these parameters. Circadian rhythm disruptions and altered sleep-wake cycles can significantly affect work performance and behavior. There has been a growing understanding that the circadian system has a major role in regulating human physiological processes, since recent studies have shown that around 80% of protein-coding genes in many tissues and organs exhibit circadian oscillations.[1] The suprachiasmatic nucleus (SCN) in the mammalian hypothalamus has been identified as the site controlling circadian behavioral rhythmicity. Lesions of the SCN abolish locomotor rhythms, and SCN transplants reinstate rhythmic behavior with the circadian properties. The oscillatory mechanism of the clock is intracellular and can be monitored.

The role of circadian rhythm genes in aging mechanisms, as confirmed by studies, state that 20-43% of genes in every human cell depend on circadian regulators.[2] Circadian rhythm genes are regular genes which regulate the cell cycle and inhibit cellular aging (an irreversible exit from the cell cycle). Aging is primarily a gradual loss of cellular and whole body capacity of responding to stress followed by reestablishment of the body to a normal state. There are some defined interventions, which give promising results in animal models or even in human studies, resulting in lifespan elongation or health span improvement. One of the most promising targets for anti-aging approaches is proteins belonging to the sirtuin family.

SIRTUIN (SIRT)-mediated deacetylation of histone H3 in K9/K14 was observed adjacent to promoters of transcription factors such as Forkhead box "O" (FOXO), E2F1, p300/CBP and PPAR.[3] Soon it was discovered that the main activity of sirtuins is deacetylation of lysine residues. This is a two-step reaction-firstly, sirtuins cleave nicotinamide adenine dinucleotide (NAD) to nicotinamide (NAM). In the salvage pathway, NAM is converted to nicotinamide mononucleotide (NMN) by nicotinamide phosphoribosyl transferase (NAMPT), a limiting enzyme for the whole pathway. NAMPT is regulated by a complex consisting of circadian locomotor output cycles kaput (CLOCK) and brain and muscle arylhydrocarbon receptor nuclear translocator-like 1 (BMAL1).[4]

The circadian clock controls the cellular process that involves the regulation of inflammation and energy hemostasis. Mice deficient in the BMAL1 circadian transcription factor have impaired circadian behavior and

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demonstrate loss of rhythmicity in the expression of target genes. These mice significantly earlier manifested age related pathologies such as inflammation of the cornea, cataracts, sarcopenia, osteoporosis, ptosis of internal organs, alopecia, reduction of visceral and subcutaneous adipose tissue, and alteration in blood composition.[5]

It was shown that SIRT1 can be found in the telomere and pericentromere regions. Telomerase is known for its ability to provide eukaryotic cells with immortality via restoring chromosome ends, which is considered a canonical function of the enzyme. Telomeres are perceived as a molecular clock that determines the longevity of cells allowing them to divide up to approximately 50 times (Hayflick limit) and that number is limited due to a replication-end problem.[6] Deletion of the Clock gene was associated with development of cataracts and extensive dermatitis rather early compared to wild type. In Clock deficient mice, a decrease in lifespan by 10% was observed. Mice with induced deficiency in Clock expression exhibit low activity of telomerase which could represent a key reason for the observed low lifespan. Telomere length undoubtedly is important for cellular aging.[7]

Recently, hitherto different studies have deciphered the roles of several clock genes like period (PER1, PER2, PER3), timeless (TIM), and cryptochrome (CRY1, CRY2) in regulating DNA damage response (DDR).[8] Timeless gene can be associated with cell cycle regulators which control aging. Timeless interacts with a cell cycle checkpoint kinase Chk1 and the ATR-ATRIP, both of which are linked to CRY2. The loss of the Tim gene results in decreased production of PER2. It was suggested that Tim is responsible for regulation of replication in the absence of DNA damage influences.[9]

The circadian clock participates in tumorigenesis by regulating downstream tumor-related genes. The period circadian regulator 1 (Per1) and period circadian regulator 2 (Per2) have been reported to be associated with the upregulation of proliferation gene Ki-67, the proto-oncogene Mdm2, the antiapoptotic gene Bcl-2, the invasion and metastasis gene MMP9, and Bax and the down regulation of Bcl-2, c-Myc, and p53 in lung, mammary, pancreatic, hepatocellular, and oral carcinoma cell lines.[10]

Disruption of circadian rhythms as a consequence of iterative alterations in lifestyle may affect well-being and normal physiological processes in humans and represents a well-known risk factor for promoting various cardio-metabolic disorders like metabolic syndrome, diabetes, and cerebrovascular disease (CVD). Humans have a significant reduction in sleeping efficiency due to circadian misalignment (shift work and eating at night), that is associated with elevated blood pressure, lower leptin levels, and higher glucose and insulin levels. Many studies have reported a strong association between evening chronotype (the tendency of a person to wake up late and sleep late) and the metabolic disease.[11] Amyloid-beta (A?) peptide levels in mouse hippocampus interstitial fluid exhibit robust daily oscillations due to Alzheimer's disease (AD) production and deposition. This peptide is responsible for the onset of cognitive decline in Alzheimer's disease patients. The circadian clock may play an important role in determining A? levels.[12]

With an increase in neurological activity, we appear to lose the ability to regulate our circadian rhythms as we age, and the master clock in the SCN appears to decline with age. The circadian system is composed of a hierarchically organized set of structures which are responsible for generating circadian rhythms and synchronizing them to the environmental conditions. Thus, circadian rhythms can be used as an aging predictor. With the advent of biobanks to ensure vast genotyping for the masses, the mapping of circadian genomics is useful to measure an account of its effect on metabolic diseases, immune system, and as an introduction to translational medicine. The widespread use of anti-oxidants must be thoroughly correlated in order to demonstrate their utility in anti-aging processes.

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