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The regulation of circadian clock by tumor necrosis factor alpha

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ABSTRACT

All organisms display circadian rhythms which are under the control of the circadian clock located in the hypothalamus at the suprachiasmatic nucleus, (SCN). The circadian rhythms allow individuals to adjust their physiological activities and daily behavior for the diurnal changes in the living environment. To achieve these, all metabolic processes are aligned with the sleep/wake and fasting/feeding cycles. Subtle changes of daily behavior or food intake can result in misalignment of circadian rhythms. This can cause development of variety of metabolic diseases and even cancer. Although light plays a pivotal role for the activation of the master clock in SCN, the peripheral secondary clocks (or non-SCN), such as melatonin, growth hormone (GH), insulin, adiponectin and Ghrelin also are important in maintaining the circadian rhythms in the brain and peripheral organs. In recent years, growing body of evidence strongly suggest that CA^{2+} signaling, tumor necrosis factor alpha (TNFα) and transforming growth factor beta (TGFβ) also play very important roles in the regulation of circadian rhythms by regulating the transcription of the clock genes.

1. Introduction

All living organisms display circadian rhythms mainly activated by physical (such as light and temperature) or metabolic signals so that organisms can align and prepare themselves to adapt for the daily changes in the living environment. In general, the circadian clock is synchronized by the patterns of light and temperature produced by the earth's rotation. In mammals, the circadian clock works within 24 h and regulates rhythms of daily physiological and cellular parameters such as blood pressure, hormone release, retinal electroretinogram (ERG) responses, body temperature, the sleep/wake and fasting/feeding cycles, metabolism, apoptosis and even cell proliferation [1–3]. As a result of these, the circadian clock mainly dictates the daily behavior and maintains homeostasis of an individual [4,5]. Although changes in light and temperature are the main drivers of synchronization, two of the most important characteristics of circadian rhythms are their persistence even in the absence of any environmental changes and the ability to be compensated against inappropriate signals such as subtle changes in light and temperature.

The circadian clock is mainly regulated or controlled by the suprachiasmatic nucleus (SCN), which is located in the hypothalamus. The SCN controls these rhythms by responding to the external changes and can reset its own phase by giving a direct response to light signals transmitted from the retina [6–8]. Although light plays a pivotal role for the activation of the master clock in the SCN, the peripheral secondary clocks (or non-SCN) also play very important roles maintaining homeostasis in the brain and the peripheral organs. The first example of a non-SCN clock is insulin. Insulin secretion from pancreatic islets display a diurnal rhythm in humans. This is consistent with the increased plasma glucose/nutrient intake during the awake/fed state. Insulin secretion stimulates glucose utilization and protein synthesis while it inhibits the beta oxidation and conversion of fatty acids into triglycerides in peripheral organs [9,10]. The second non-SCN clock is Ghrelin, a peptide hormone produced by the gastrointestinal tract which functions as a neuropeptide and regulates appetite. Ghrelin is secreted when the stomach is empty. It acts on the hypothalamic cells of the brain to induce the secretion of gastric acid which helps digestion of food. Therefore, Ghrelin plays significant role in the regulation of energy homeostasis [11–13]. The third non-SCN clock is Melatonin. Melatonin is produced and secreted from the pineal gland. Its synthesis is very tightly controlled by the suprachiasmatic nucleus (SCN) region of the hypothalamus. Increased production of Melatonin during night time and almost complete inhibition during day time is one of the best examples of light dependent SCN-mediated regulations of non-SCN clock [14–16]. The forth non-SCN clock is adiponectin. The expression of adiponectin is also dependent on the circadian clock. Adiponectin

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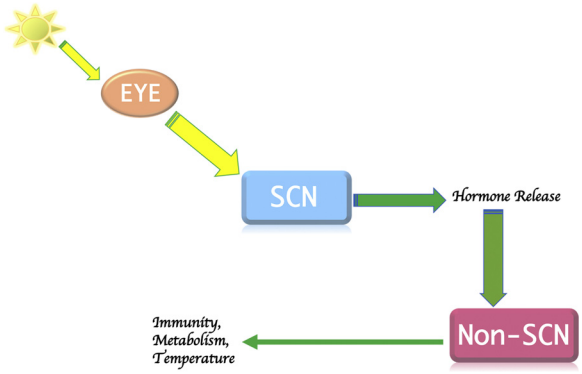

Fig. 1. The Circadian Clock is a dynamic system and mainly controlled by light. Light-induced activation of SCN (Suprachiasmatic Nucleus) causes release of metabolic hormones which establish Non-SCN (Non-Suprachiasmatic Nucleus) at peripheral organs and regulate homeostasis.

expression is generally induced later in the afternoon and plays a very important role in increasing insulin sensitivity. Although we don't know the actual mechanism as to why it is induced in the afternoon, it is likely that induced adiponectin helps maintain glucose utilization at night time by elevating insulin levels and actions [17,18]. The fifth non-SCN clock is Growth Hormone (GH), which is produced in the anterior pituitary gland. While synthesis and secretion of GH is induced by GH releasing hormone (GHRH), its synthesis is inhibited by somatostatin (SMS) [19,20]. Unlike insulin, GH decreases the utilization of glucose and increases lipolysis. The synthesis and secretion of GH is regulated by circadian and ultradian variations. Unlike other hormones, the expression of GH shows more non-discrete peaks of more uniform amplitude throughout the day in females compared to males and its expression is induced at night in both genders [19–22] (Fig. 1).

Although the circadian rhythms can control our daily life/behavior, it can be easily be modified by unanticipated changes in our behavior and food intake. Sometimes adjustment to these subtle changes can be difficult. For example, activation of the metabolism during unusual times with food intake can try to reset the phase of peripheral clocks. If reset is not effectively accomplished, this can cause circadian deregulation of peripheral clocks and potentially induce desynchronization of the metabolic regulation resulting in the development of diabetes and obesity. Similar to this, desynchronization of the circadian clock in shift workers such as frequent flyers such as pilots can have serious outcomes for these people and prone them to develop metabolic disorders and even cancer [23–27]. Therefore, understanding the mechanisms molecular regulations within the circadian rhythm are significant in coping with the outcomes of the desynchronization of the circadian clock.

1.1. The molecular mechanism of regulation of circadian clock

According to most recent literature, the regulation of the circadian clock is mainly regulated by transcriptional-translational feedback loops. The two genes, CLOCK (circadian locomotor output cycles kaput) and BMAL1 (brain and muscle arntl-like protein 1) are positive regulators, while PER and CRY proteins are negative regulators of the circadian clock. When signals are generated in SCN or at non-SCN clock, CLOCK1 and BMAL1 are activated by forming a hetero-dimer and bind to E-boxes (5′-CACGTG-3′ or 5′-CACGTT-3′) in the promoters of target genes [28–31]. With this binding, CLOCK:BMAL1 heterodimer recruits histone acetyl transferases (HATs) such as p300, PCAF and CBP to this complex and induces acetylation of histones (H3 and H4) at target genes [28–34]. In addition to this, the CLOCK:BMAL1 complex recruits JARID1a, HDAC inhibitors to the complex and this further augments the rate of transcriptional induction [35]. According to the results of most recently conducted studies, the establishment of the circadian rhythm are mediated by transcriptional induction of roughly hundreds of genes. Of these, roughly 350 are induced in the SCN as well as in the liver and only 28–37 of them overlap [32,33,36–38]. Of these target genes, PER and CRY (the negative limb proteins) are also transcriptional targets of CLOCK:BMAL1 dimer. Once induced, these proteins function as a negative regulator of the circadian clock by binding to CLOCK and BMAL1 proteins and prevent them to form CLOCK:-BMAL1 heterodimer, therefore PER and CRY gene products form a negative feedback loop mechanism for the activation the circadian clock and establish repressive state [38–42]. The recruitment of histone deacetylase SIRT1 also negatively regulates the circadian gene expression by deacetylating the components of transcriptome formed by CLOCK and BMAL1 as well as modulating CLOCK-mediated chromosome remodeling [43–46].

Since PER and CRY gene products negatively regulate the circadian clock, the initiation of the next cycle of circadian rhythm depends on the inactivation of PER and CRY proteins. This is achieved by phosphorylation-dependent degradation of Per and CRY gene products. PER protein is phosphorylated by casein kinase 1ε (CK1ε) and CK1δ. CRY1 is phosphorylated by AMPK1 and CRY2 is phosphorylated by DYRK1A/GSK-3β cascade. The phosphorylated PER and CRY proteins are ubiquitinated by βTrCP and F-box gene Fbxl3 product, respectively, and degraded by proteasome [47–56]. Therefore, proteasome-mediated degradation of these proteins is a must in order to terminate the repression phase and initiate a new cycle of transcription. The second feedback loop induced by CLOCK:BMAL1 dimer is the transcriptional induction of the orphan nuclear-receptor genes Rev-Erb α/β and RORα/β/. Once induced, these nuclear receptors bind to Retinoic acid-related Orphan receptor Response Element (RORE) binding sites within the promoter of Bmal1 gene and Rev-Erb α/β and RORα/β/ regulate BMAL1 transcription negatively and positively, respectively. Therefore, these proteins negatively regulate the formation of CLOCK:BMAL1 heterodimer and the activation of circadian clock [57–60]. **(**Fig. 2**).**

1.2. Regulation of the circadian clock by tumor necrosis factor alpha, TNFα

TNFα is a pleiotropic cytokine which plays pivotal role in regulation of apoptosis, inflammation and immunity. Dysregulation of TNFα causes several diseases such as rheumatoid arthritis, major depression, inflammatory bowel disease, cardiovascular disease, type 2 diabetes and cancer [61,62]. TNF-α activates several signaling pathways by binding to its receptors TNFR1 and TNFR2. When TNFR1 was first discovered many believed that the main function of this receptor would be the induction of apoptosis because of the presence of death domain (DD) [63]. Today, however, we know that TNFR1 signaling can induce diverse signaling events which result in activation NF-kB as well as caspase-8, which promote growth and apoptosis, respectively [64,65].

In general, TNFα exerts its biological effects by binding to two different receptors, TNFR1 and TNFR2. TNFR1 is a 55 kD trans-membrane protein with the death domain (DD) on its cytoplasmic domain and which is responsible for the majority of TNFα by mediating protein-protein interactions. The proteins shown to bind to the death domain of TNFR1 are, TNF-receptor associated death domain (TRADD) and receptor-interacting protein-1 (RIP1), both of which also possess death domain.

While the binding of TRADD to TNFR1 recruits the Fas-associated death domain and procaspase 8 into a complex that initiates apoptotic caspase cascade, the binding of TRADD to RIP1 and TNFR-associated factor 2 (TRAF2) induces formation of complex-1 [66–68]. Complex-1 is composed of RIP1 (receptor-interacting serine-threonine kinase 1), TRAF2 (TNF-receptor associated factor-2), cIAP1/2 (cellular inhibitor of apoptosis protein 1/2, LUBAC (linear ubiquitin chain assembly complex) and TAK1 (transforming growth factor-activated kinase-1) [69–72]. In this complex, a step-wise ubiquitin network is established and in this complex TRAF2, cIAP1 and cIAP2 introduces Lys63-linked ubiquitination on RIP1, NEMO, TRAF2 and TAK1. Following these ubiquitylations, LUBAC complex introduce Met1-linked linear ubiquitin

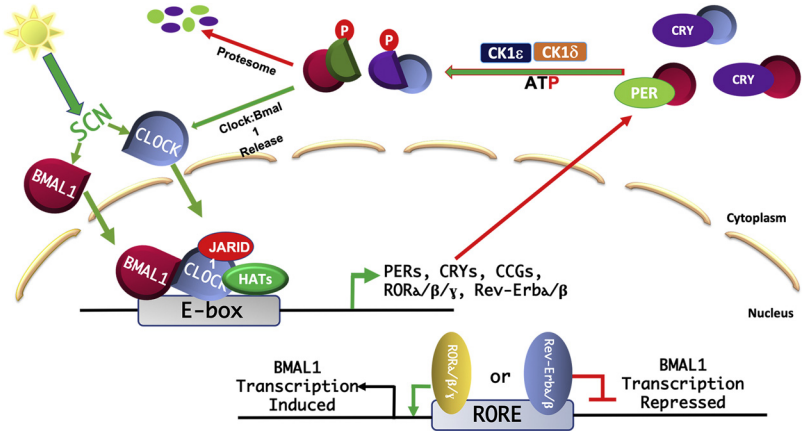

Fig. 2. The circadian clock is regulated by CLOCK and BMAL1 genes. When signals are generated in SCN or at non-SCN clock, CLOCK1 and BMAL1 are activated by forming heterodimer and bind to E-boxes (5′-CACGTG-3′ or 5′-CACGTT-3′) in the promoters of target genes and recruits histone acetyl transferases (HATs) such as p300, PCAF and CBP to this complex, then HATs induces acetylation of histones and activate transcription. In addition to inducing the expression of over 400 genes, whose products establish circadian rhythms, CLOCK:BMAL1 heterodimer also induces the transcription of PER and CRY genes whose products bind to CLOCK and BMAL1 proteins and prevent them forming heterodimer. In addition to PER and CRY genes induction, CLOCK:BMAL1 heterodimer also induces the expression of orphan nuclear-receptor Rev-Erb α/β and RORα/β/. Once induced, these bind to Orphan Receptor Response Element (RORE) of BMAL1 gene and induces or repress its transcription, respectively, therefore, negatively and positively regulate the formation of CLOCK:BMAL1 heterodimer. To re-initiate the circadian clock, CK1e and CK1d phosphorylate PER and CRY proteins, and induce their degradation by proteasome, thereby releasing Clock and Bmal1 proteins.

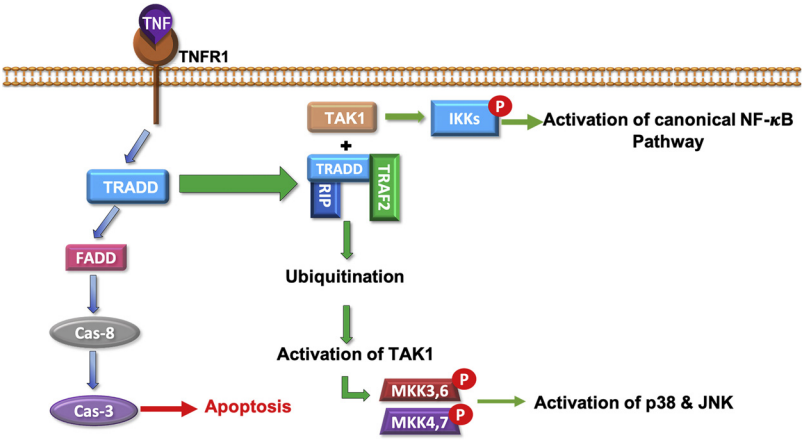

Fig. 3. Binding of TNF to TNFR1 initiates formation of different signaling complexes. TNFR1 binds to TRADD and RIP1 via death domain. While formation of TNFR1-TRADD-FADD-Caspase-8 induces activation of caspase-8 and induces apoptosis by activating casapase-3, formation of TNFR1-RIP1-TRAF2 and subsequent ubiquitination of RIP1 recruits and induces ubiquitination and activation of TAK1 (TGF beta-activated kinase 1). Activated TAK1 induces phosphorylation of IKKs and MKK3,4,6 and 7. Activated MKKs phosphorylate and activate p38 and JNK kinases. As a result of this phosphorylation cascade activated NF-kB and p38 and JNKs induces expression of TNF-responsive genes.

chains to RIP1, NEMO and TAK1, and all these results in stabilization of complex-1. In this complex, TAK1 is activated and activated TAK1 phosphorylates and activates MKK3,6 and MKK4,7. Activated MAPKKs phosphorylate and activate mitogen-activated protein kinase (MAPK) cascade resulting in activation of p38 and JNK kinases. At the same time, TAK1 also phosphorylates and activates IKKβ which induces the activation of canonical NF-kB pathway by phosphorylating IkBs [73–79] (Fig. 3).

Similar to endocrine hormones, the circadian clock also controls rhythmic expression of cytokines and activation of blood cells by controlling both innate and adaptive branches of immunity. Among these cytokines, TNFα is particularly important because of its active involvement in the activation of both innate and adaptive branch of immunity by activating NF-kB [80,81]. TNFα expressions show regional differences in the brain and its expression is at the highest level in the hypothalamus, hippocampus, and cerebral cortex at the beginning of the light phase in rats [82,83]. The sleep-wake period not only regulates the expression of TNFα, but also induces the expression of its receptor, TNFR1 in mice [84]. The circadian rhythm-dependent induction of TNFα in the hypothalamus, hippocampus, and cerebral cortex is not a coincidence, because, induced TNFα and its receptor play significant roles by regulating the expression of Per1,2 and 3 *in vitro* and *in vivo* in mice [85]. By suppressing the expression of PER genes, TNFα interferes with the regulation of the circadian clock and causes prolonged rest periods in the dark. This process is associated with development of autoimmune diseases and fatigue [86].

1.3. CA^{2+} signaling, circadian clock and TNF-α

Calcium is an important second messenger and plays a crucial in regulating the clock gene expression. However, the intracellular calcium rhythms is regulated by the circadian clock [87,88]. Several studies have shown that TNFα protects neurons and against metabolic-excitotoxic insults by promoting maintenance of calcium homeostasis [89]. Although TNFα represses the transcription of Per1, 2 and 3 it also contributes to the induction of the circadian rhythm by inducing the transcription of BMAL1 gene and RoRα by calcium-dependent manner [90]. Moreover, it was also shown that Ca^{2+} influx is essential for the expression of Per1/2 genes [91]. Taken together, these results indicate that TNFα plays both positive and negative roles in the regulation of the circadian clock by inducing calcium influx or maintaining high cellular level of calcium and inducing expression of BMAL1, but at the same time TNFα-mediated induction of calcium accumulation induces expression of Per1/2 genes [90–92].

It is well known that as a secondary messenger, calcium influx also induces phosphorylation of transcription factor CREB and in the SCN and periphery phosphorylated CREB induces the transcription of Per1 gene by binding to the CRE regions of the promoter of Per1 gene [93,94]. The results indicate that Calcium influx have significant roles in both the induction and the repression of the circadian clock. It does so by inducing the expression of BMAL1 as well as PER genes.

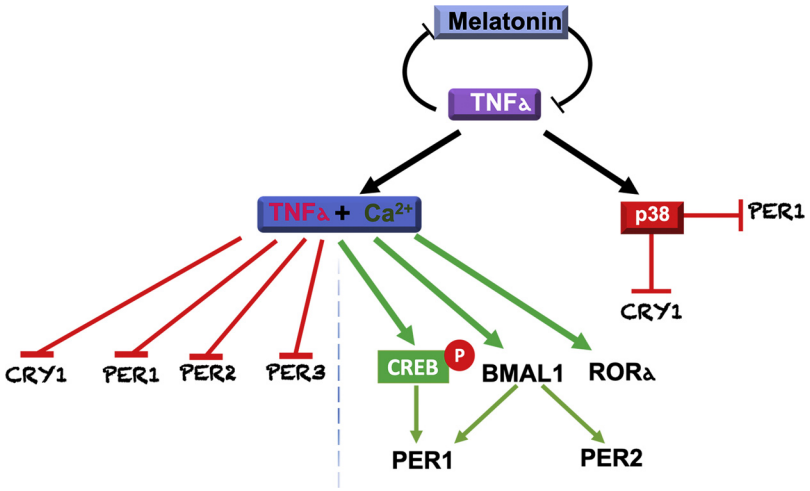

Fig. 4. The circadian rhythm-dependent induction of TNF alpha in the hypothalamus, hippocampus, and cerebral cortex plays significant role in regulation of circadian-rhythm. Induced TNF alpha suppresses the expression Per1,2,3 and Cry1 genes by activating p38 MAPK, therefore causes prolonged rest periods in the dark. However, in addition to repressing PER and CRY gene transcription, TNF alpha also induces Calcium influx which causes CREB1 phosphorylation and Bmal1 induction. Also, there is a negative feed-back loop between Melatonin and TNF alpha. Whereas TNF alpha-induced suppression of melatonin synthesis prolongs rest period, Melatonin-induced TNF alpha suppression induces sleep period. As a result, TNF alpha controls circadian rhythm in both positive and negative way.

1.4. TNFα-mediated repression of the circadian clock requires p38 MAPK activation

Mitogen-activated protein kinases (MAPKs) are highly conserved in eukaryotes and work both as an output and input in the control of the circadian clock [95]. Since p38 is activated by TNFα very effectively, in a sense, the role of TNFα in regulation of the circadian clock is partly depended on its ability to activate p38 MAPK [96]. Studies conducted in rodents have shown that p38 MAPK pathway plays a crucial role in the response to light in the SCN. In addition to the rodents, it has also been shown that p38 MAPK activity was necessary for photic resetting of clock rhythm in the chick pineal gland and as well as in the cultured Xenopus retina [97–100]. Although the involvement of p38 activity in photic resetting is essential, it is unclear whether TNFα is also required for this. However, it has been shown that TNFα-induced transcriptional repression of PER1 and CRY1 genes require TNFα-induced activation of p38 as well as calcium accumulation by TNFα [92].

1.5. Melatonin, circadian clock and TNF-α

Melatonin (N-acetyl-5-methoxytryptamine) is synthesized by the pineal gland at night and plays pivotal role in the control of controls circadian rhythms. In mammals, melatonin function as a major hormonal output and distributes temporal signals generated by the SCN to the targets tissue expressing melatonin receptors [101]. The synthesis and release of melatonin by the pineal gland is inhibited by light exposure. Since the SCN also has receptor for melatonin, melatonin can feedback onto the Circadian clock. In healthy humans, melatonin secretion starts between 9:00 p.m. and 11:00 p.m., and serum levels reach to peak levels between 1:00 a.m. and 3:00 a.m. [102]. Since melatonin can transmits the signals of SCN to the non-SCN clock expressing melatonin receptor, and also affect the SCN itself, induction or repression of melatonin synthesis directly affect the daily circadian rhythms. Several studies have shown that melatonin modulates the inflammatory response and also affected from cytokines such as TNFα [103,104]. It has been shown that TNFα treatment inhibits the transcription of Aa-nat gene, whose product is the key enzyme in melatonin biosynthesis. This inhibition was transient. Therefore, it was suggested that the accumulation of TNFα during sepsis or under inflammatory conditions can interfere with the nocturnal surge of melatonin for short period of time. This study provides a type of mechanism of the molecular pathways affecting pineal activity during inflammatory responses [104]. In addition to the repressive effect of TNFα on melatonin synthesis, melatonin also inhibits the production of TNFα under both *in vitro* and *in vivo* conditions. It not only inhibits the synthesis of TNFα but can reverse the effect of t TNFα [105–107].

Anti-TNFα activity of melatonin also explains its anti-cachectic activity of melatonin and help us to better understand why people who have chronic immunoinflammatory diseases are influenced by psychoemotional factors. In another study, levels of melatonin and TNFα were compared in the colostrum and milk from mothers who gave birth by vaginal or cesarean. It was shown that nocturnal melatonin increases 3 days after vaginal delivery. While the increase in melatonin concentration in the colostrum of mothers who delivered vaginally was significantly higher, there was no significant difference of diurnal and nocturnal melatonin secretion in the colostrum of mother who delivered by cesarean. To explain why melatonin level did not increase in the colostrum of mother, they found high levels of TNFα in the colostrum and milk of the mother who gave birth by cesarean. It was suggested that physical injury caused by cesarean increased TNFα secretion as a result of immune activation and this caused suppression of nocturnal melatonin synthesis [104]. This study was further supported with an unrelated incidence where it was shown that injury inhibited melatonin production from endocrine pineal gland as well as from the colostrum phagocytes [108].

Another physio pathological condition under which melatonin secretion is severely affected is the development of sepsis. It was shown that in the early stages of septic conditions the expression level of Cry1 and Per1 genes were decreased while the expression of TNFα is highly upregulated, based on these, it was suggested that increased TNFα causes repression of Cry1 and Per1 genes, as a result interferes with negative feedback loop of the circadian clock and suppresses melatonin secretion and circadian gene expression [109] (Fig. 4).

1.5.1. The circadian clock, TGFβ and TNFα axis

TGF is also an important regulator of the circadian clock. It has been shown that adenovirus-mediated ectopic expression of TGFβ significantly induced the expression of BMAL1 and NPAS2. However, it strongly suppressed the expressions of Per1, Per2, Per3, Rev-erbα, RORα and DBP [110]. Therefore, increased TGFβ expression represses the expression negative regulators of the circadian clock and can prolong the wake period [110]. In addition to this, it was also shown that TNFα and TGFβ reduce the expression of cold inducible RNA-binding protein (CIRBP), which is required for circadian gene expression, in fibroblasts and neuronal cells [111]. The Cirbp protein is constitutively expressed in the hippocampus, and cerebral cortex as well as in testis, lung, heart, kidney. Its expression is up-regulated and released from macrophages by stress, cold (32 °C) and by hypoxic conditions. The up-regulated Cirbp protein protects the body by triggering inflammatory responses by binding to TLR4 and also induce the expression of circadian clock genes under hemorrhagic shock and sepsis [111–113]. Therefore, controlling the expression of CIRBP gene is very important

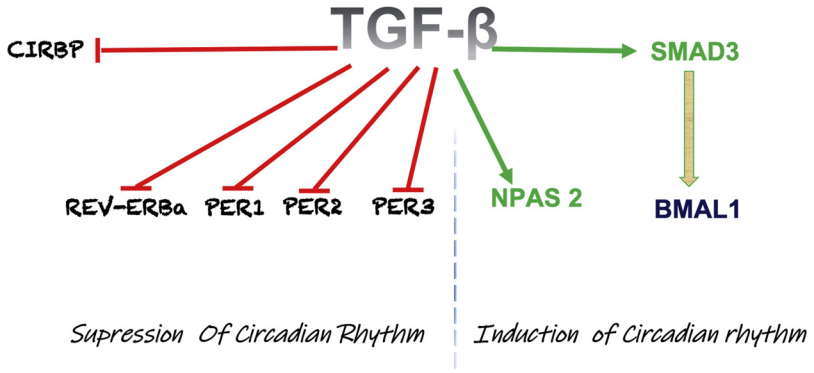

Fig. 5. TGF alpha plays important role in regulation of circadian rhythm by repressing the expression of negative-regulators of circadian clock, therefore, can prolong the wake period and can reverse the wake period by inducing the expression of BMAL1 gene by activating transcription factor SMAD3.

against cold and septic shock, and its down-regulation by TNFα and TGFβ can not only alter circadian rhythms but also weakens the bodies defense during cold. Recently, it was shown that the expression of TGFβ-activated transcription factor Smad3 displays similar expression patterns with BMAL1 and Smad3 functions as an upstream of Bmal1, explaining how TGFβ induces expression of Bmal1 [114]. Overall, these results indicate that TGFβ plays crucial roles in the regulation of the circadian rhythms by regulating the expression of both positive and negative oscillators of circadian clock (Fig. 5).

2. Conclusion

The circadian rhythm functions within a 24-hour period and maintains number of cellular events such as sleep/awake, metabolic activities, hormonal regulation, body temperature, apoptosis and cell cycle [1–3]. The circadian rhythm is mainly controlled by Suprachiasmatic nucleus (SCN), which is located in the anterior of hypothalamus, and responds to external changes, such as light and temperature [115]. In addition to SCN, peripheral clocks (or non-SCN) which are represented by hormones secreted from liver, heart, kidney, adipose tissue and pancreas also play significant role to convey the signals initiated by SCN [116,117]. Recent evidences have also shown that the circadian clock not only regulates immune responses, but also is regulated by the components of immune system, in other words, the communication between the immune system and the circadian clock is bidirectional [85,118–120]. Although several immunomodulator cytokines play an important role in this, recent evidences strongly indicate that TNFα functions as bridging element between the circadian clock/immune system. Since sleep-wake period regulates the expression of TNFα as well as its receptor, activation of TNFα signaling is used to contributes to the induction of the circadian rhythm by repressing the transcription of PER genes. Therefore, prolonged expression of TNFα due to chronic infections and daily stress-inducing conditions shifts the balance of sleep/wake period toward prolonged rest periods. Ultimately, this results in development of several serious diseases. In fact, several studies have shown that desynchronization of circadian clock in respect to the environment showed significant correlation between desynchronization of circadian clock and higher incidence of development of several types of cancer including but not limited to breast, colon, prostate, endometrial and non-Hodgkin lymphomas [121–125].

Declaration of conflict of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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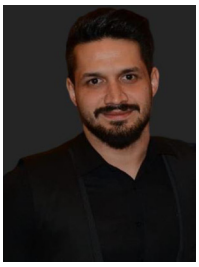

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