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Non-coding Vibration in Circadian Oscillation

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Abstract

Neuron driven physiological activities such as sleep, feeding, energy consumption are controlled by light sensitive central clock genes in the pacemaker neurons in the brain. Multiple epigenetic events including post-transcriptional regulation, splicing, polyadenylation, mature mRNA editing and stability of translation products are the main vibrators for circadian oscillation with the instructive role of various sets of non-coding small regulatory RNA. Here, we sum up the basic role of small regulatory RNA and their epigenetic circuits in brain clock activity.

Keywords: Circadian rhythm; RNA interference; microRNA; Long non-coding RNA; Biological clock

What is Circadian Rhythm?

Most living organisms possess internal clock with a circadian rhythm of 24 h approximately. The biological core clock that regulates basic physiological activities like the asleep-wakefulness cycle, metabolism, energy consumption, hormone secretion is maintained by photo-regulated clock genes in pace-maker neuron [1]. The core clock mechanism also results in several rhythmic behavioral expressions like seasonal reproduction where animals senses spring with their internal clock and start to show reproductive behavior (Figure 1) [2].

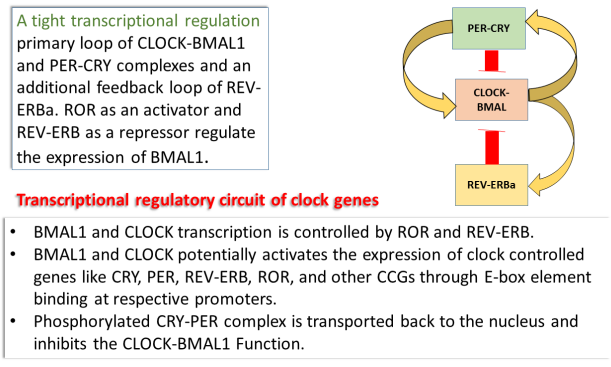

Figure 1: Transcriptional regulatory circuit of clock genes.

Biological rhythm can be endogenous as well as exogenous [3]. The change in the magnitude of activity is known as amplitude. The time span of a complete rhythmic cycle is called period. When the environmental cues are taken from the environment, synchrony is established and maintained. This is known as entrainment. This entrainment mediated rhythmic behavior is called circadian rhythm [4,5]. The biological clock is self-sustainable as well as it can exist without environmental cues too. The rhythmic cycle is of four types viz., ultradian, infradian, lunar and circannual rhythm [6]. An external cue known as zeitgeber keeps a track on this biological rhythm [7]. It regulates the behavior of the organism. Daylight is the primary cue, which resets circadian clock [8]. Researchers have hypothesized that biological clock is consists of time-keeping apparatus, entrainment pathway and a core component of the biological clock [9]. They are operated in a serial fashion where the entrainment pathway transmits environmental cues to the timekeeping apparatus; an environment independent oscillator. Finally, the core component activation by the circadian oscillator is done at specific points of time in circadian rhythm (Figure 2) [10,11].

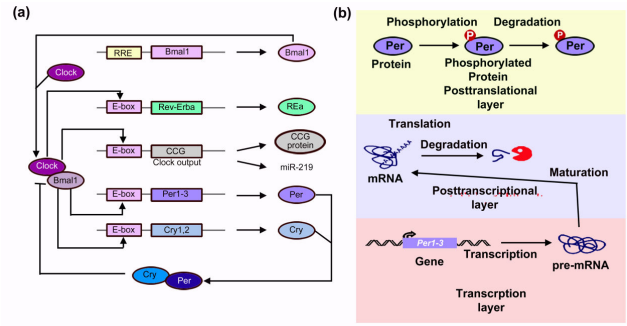

Figure 2: The figure shows mammalian circadian clock and other three layers of its control. (a) Suprachiasmatic nucleus possess master circadian pacemaker. Role of Clock-Bmal1 complexes in transcription of Per, Cry, Rev-Reba. Two negative feedback loop are established through oscillatory activity of Clock-Bmal1 complex. (b) Correlation between transcriptional, post-transcriptional and post translational steps in regulation of Per gene expression. Per proteins regulates the formation and activity of Clock-Bmal1 complex. This complex regulates the levels of per proteins at the level of transcription (yellow). They are also regulated at post translational level (Blue). The regulator of oscillations like Transcription, mRNA Translation and degradation are shown in the figure.

Major Regulatory RNAs in Circadian Rhythm

snRNA and snoRNA

Small nuclear RNAs (snRNAs) consisting of 80 to 350 nucleotides are found not only in human but also in other eukaryotic model organisms like *Caenorhabditis elegans*, Baker's yeast, etc. as part of ribonucleoprotein (RNP) complexes [4]. snRNAs like U1, U2, U4, U5 and U6 are major players in RNA splicing and also involved in several RNA-RNA and RNA-protein interactions in the canonical assembly [12]. Less abundant snRNAs viz. U11, U12, U4 atac and U6 atac along with U5 form a variant "minor" spliceosome termed U12-type19 [8]. A number of small RNAs were localized to the nucleolus, which was used for guiding the methylation and pseudo-uridylation of several other small RNA-liker RNA, tRNA, and snRNA [13]. Moreover, due to differential expression, snoRNA can play as regulatory RNA as it may target a vast range of RNAs [14]. Studies have shown that diurnal cycling noncoding RNAs like UsnoRNA host genes (USGS) encode precursors of more than 50 box-C/D small nucleolar RNAs as well as the key regulators of ribosomal biosynthesis. Transcriptional profiling study of an exon shows that either period or circadian time regulates the abundance of alternative splice isoforms for several genes [15]. However, loss of function of period alters the RNA editing frequency moderately at different editing sites. A correlation between RNA editing and a key circadian gene are suggested by this data [14].

microRNAs

Recent studies have suggested a role of miRNA in modulating circadian clock. The two major miRNA viz. miRNA-132 and miRNA-219 were thoroughly studied. Experimental data suggested that miR-219-1 is a clock-controlled gene and CREB-regulated gene miR132 shows light-inducible expression which requires the involvement of ERK/MAPK cascade mechanism [16,17]. *In vitro* reporter assay gives conclusive data about miRNA-132 and miRNA-219 as positive controller of CLOCK and BMAL1-dependent Per1 expression [18]. Experimental data proves that miRNAs present in Supra Chaismatic Nucleus (SCN) can be photo-regulated as well as can be controlled by the molecular clock [19]. Daily express levels of two other miRNAs, miR-263a and miR-263b changes rigorously in wild-type flies, whereas miR-279 targets a ligand of the JAK/STAT pathway to influence circadian behavior [20]. In addition, oscillation of miRNA 959-964 cluster plays a critical role in Drosophila feeding time and circadian rhythm [21].

Long ncRNAs

Long ncRNAs (lncRNAs) are a novel family of functionally active RNAs, which regulate gene expression by a cascade mechanism [22]. The mechanism involves recruiting epigenetic modifiers, controlling mRNA half-life and regulating transcription factors. They are also involved in circadian rhythm especially in vertebrates [23]. 112 lncRNAs showed differential expression of night/day in rat's pineal gland, the source of melatonin, among which half of this alteration results increase in nocturnality [24,25]. Light exposure at night can rapidly reverse the abundance of a number of lncRNAs. Organ culture studies suggested that the expressions of lncRNAs are regulated by norepinephrine through the involvement of cAMP [14].

Circadian Rhythms and Dynamic Post-Transcriptional Controls

Post-transcriptional control of circadian rhythm was first demonstrated in Drosophila [26,27]. Subsequently, the stability of oscillating mRNA during circadian rhythm was also explained in core pacemaker component in mammals [28,29]. However, in mice, the stability of Per2 and Cry1 mRNAs is altered during the period and collectively with oscillating transcription; it shows rhythmic alteration in mRNA level [30]. Woo et al. have shown that the interaction of RNA binding proteins Ptbp1 and Hnrpd help in the binding of 3' UTRs, Per2 and Cry1 mRNAs and cause prompt degradation [31]. The cytoplasmic levels of Ptb1 and Hnrpd regulate over the circadian rhythm and interact with decay rates of the target mRNA [32]. It has been shown in synchronized cultured cell that the Per2 and Cry1 mRNA oscillations were readily affected during RNAi-mediated reduction of Ptbp1 and Hrpd levels. These findings conclude that the level of oscillation of cytoplasmic RNA-binding proteins could be a potential candidate for the oscillating stability of targeted mRNA. It ultimately directs the levels of oscillation of encoded proteins [33].

Generation of Cyclic Post-Transcriptional Controls

Generation of cyclical post-transcriptional controls is observed by different mRNAs and also in different physiological systems [34,35]. Several factors are uniformly expressed which are actively involved in RNA regulations. Surprisingly the sub-cellular localization and activity of these factors oscillate readily. However, the molecular mechanism of the oscillation is not known yet [36]. In Neurospora crassa several proteins like FRQ, FRH help in the formation of FFC complex that recruits RNA exosomes to frq mRNA, which leads to degradation of FFC complex [37]. Along with the capacity of FFC to repress the frq gene transcription forms the negative feedback loop, which ultimately leads to the generation of circadian oscillations [38,39]. AtGRP7 and AtGRP8 are RNA binding proteins present in Arabidopsis thaliana possess circadian expression. Overexpression of AtGRP7 ablates expression of Atgrp7 and Atgrp8 mRNAs. These two proteins can interact with their respective pre-mRNAs. Thus their splicing pathways towards premature termination codon-containing mRNA isoforms are readily activated [40]. Degradation of these isoforms occurs via nonsense-mediated mRNA decay (NMD) Pathway. As a result, AtGRP7 and AtGRP8 negatively auto-regulates as well as cross-regulate their synthesis. The above-said machinery probably suggests cyclic destabilization of AtGRP7 and AtGRP8 mRNAs which mediates circadian oscillations [41].

Role of Non-Cyclic Post-Transcriptional Controls in Circadian Rhythms

Successive activation and repression of gene expression are regulated by a transcriptional negative feedback loop [42]. After the offset of transcription, mRNA decay follows exponential kinetics. If the half-life of respective mRNA is short then the decay will be considerably rapid with respect to the time of transcriptional oscillations [43,44]. As a result, the mRNA will be removed before the transcription re-commences and high level of mRNA oscillation is produced. So it is necessary to degrade mRNA for conversion of switches [43].

Future Outlook

In retrospect, numerous fundamental small regulatory RNAs that operates the epigenetic expression including genetic reprogramming of genome organization. Each genome is tuned by numerous small regulatory RNAs that coherently orchestrate the epigenetic trajectories during brain and CNS development and differentiation. Multiple landscapes and small regulatory RNAs are the fundamental part of overlapping, intergenic, intronic sense-antisense, small RNAs with interlaced exons which control promoter activities, splicing patterns, polyadenylation sites during developmental processes.

Indeed, RNAs can fold in multiple complex forms and allosterically responsive multi-dimensional structures that are involved in protein bindings and other RNA-DNA duplex or triplex formations. This RNA may interact with multiple unrelated well-characterized motifs and functional domains of various proteins. The multiple functions of brain development and pacemaker neurons are underway in many neuro-genetics laboratories. The epigenetic post-transcriptional control also acts on circadian rhythms in different angles and various ranges in the brain.

Authors' Contributions

PP wrote the initial paper and UB designed the mini review and rewrote and finalized the paper. MPB and UB drafted finally or revised the manuscript and all authors approved the final version.

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Competing Interests

The authors declare that they do not have any competing interests.

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