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Circadian Clock Regulation through Pre-mRNA Splicing: A Review

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A B S T R A C T

Alternative splicing has a crucial role in the regulation of gene functions and enhancement of the proteome diversity in plants. In plants especially Arabidopsis, introns are present in most of the genes. A significant number of the intron-split genes concerned with the regulation of different biological events counting the circadian clock are alternatively spliced. In this current review, our main aim is to study the participation of alternative splicing in the circadian clock regulation.

Introduction

The earth undergoes rotation while revolving around the sun. This is responsible for alteration is of light and dark periods leading to variation in temperature. The variation of day length in different locations has been reported due to the changing of the sun's positions to the earth's axis. The mechanism that is responsible for the prediction of such light and dark alterations is referred to as the biological clock, or in a more scientific term, the *circadian clock* after the Latin, "c*irca diem*", meaning "around or about a day". The "clock" works in a rhythm of about 24 hours indicating the time of day, which is almost indicative of the length of the day. On the other hand, seasonal variations can also be estimated by calculating day length, which is very highly significant both at the equator and higher latitudes. Erwin Bunning, a German plant physiologist researched circadian rhythms and concluded that these rhythms have an adaptive value (Bünning, 1964).

History of the plant clock

In plants, molecular research picked up the pace when Steve Kay and Andrew Millar introduced the firefly *Luciferase* (*LUC*)

reporter gene, fused with the photosynthesis gene *Chlorophyll A/B Binding Protein 2* (*CAB2*) (Millar and Kay, 1991) into the model plant *Arabidopsis thaliana*. *CAB2* expression has been reported to be regulated both by the circadian clock as well as by the phytochrome (phy) photoreceptors (Millar and Kay, 1991; Anderson *et al.*, 1994). Photosynthesis is an important physiological process responsible for plant growth connecting a large number of plant circadian rhythms (Millar, 1999).

The possible task of the clock in the light-harvesting process is to anticipate the light period to get the plant ready for photosynthesis. Hence, energy uptake efficiency throughout the day has been enhanced by having the photosynthetic machinery being activated from the first light. The circadian clock has a significant role in regulating the different metabolic and developmental events to the most favorable time of the day, thereby enhancing the probability of growth and chance of survival of microorganisms (Blasing *et al.*, 2005; Dodd *et al.*, 2005).

Genetics of plant clock

Most of the attempts to reveal different mechanisms of biological clocks in different species have been conducted on mutants having phenotypes with a malfunctioning clock. Mutants developed through different forward and reverse genetic approaches led to the discovery of genes coding for proteins having normal circadian rhythms. In forward genetics, the selection is based upon a phenotype. In clock research, a changed phase of clock regulated gene expression is a breeding objective. In reverse genetics, selection of traits is done from genotype to phenotype and accordingly effect of gene manipulation is studied. Through mutational analyses, complex systems are studied by alterations of a single component while keeping all other parts constant (Dunlap, 1993). On the other hand, the resulting phenotype is formed due to the interaction of many factors. Such genetic studies are intended towards providing insight into the rhythmic biochemistry of the biological clock (Dunlap, 1993).

Screening of the mutants having relevant phenotypes is comparatively easier. On the other hand, it is more challenging to define the function of the mutated gene within the clock system. Based upon the locus of the induced mutation within a gene, there can be considerable variation in phenotype, e.g. *toc1-1* mutants have a phenotype that is dependent to light, but not the *toc1-2* mutants (Millar *et al.*, 1995; Somers *et al.*, 1998; Strayer *et al.*, 2000; Más *et al.*, 2003). The most significant example of such type of mutant is a gene knock-out, in which the mutation or insertion is frequently located within an exon and hence drastically affects transcription/ translation.

However, non-functional mutants may also be obtained, in which transcription of the mutated gene might take place, its wild-type function is not possible. For example, a synthesized protein may not bind with its substrate due to a conformational change in the protein or lack of phosphorylation. A third type is a mutant with gain-in-function, in which the mutated gene/protein gains a new function, for instance, over-expression mutants, may constantly promote expression of another protein.

It is not easy to predict the sorts of mutagenesis taken up by clock mutant from their clock phenotypes. A knock-out disrupts the rhythm in no way, there is the shortening of increasing phase and/or period. To disrupt the clock completely, several genes have to be knocked-out or they need to over-express the

right component (Wang and Tobin, 1998; Ding *et al.,* 2007). An additional factor to consider is the timing; to disrupt the interaction between two proteins at a certain time of day may lead to an out-of-phase clock, while at protein levels remain there no change. Bearing all these variables in mind, it is highly challenging to firmly establish mutation types and their effects, for defining a new piece of the clock machinery.

Pre-mRNA splicing machinery: the spliceosome

mRNA is produced as a precursor mRNA (pre-mRNA) during the process of transcription in the nucleus (Wahl *et al.,* 2009). There, it undergoes a series of processing steps before being transported to the cytoplasm where it serves as a template for protein biosynthesis and is degraded eventually (Wahl *et al.,* 2009).

One of the processing steps is the elimination of introns from the intron-containing pre-mRNAs, which is termed pre-mRNA splicing. In eukaryotes, pre-mRNA splicing is one of the fundamental processes in constitutive and regulated gene expression, as most genes typically contain multiple introns (Moore and Proudfoot, 2009).

The removal of introns from the pre-mRNA is involved in sequential phosphodiester transfer reactions which are catalyzed by the spliceosome, a large ribonucleoprotein (RNP) complex (Wang and Burge, 2008). The spliceosome is one of the most complex machines in the cell (Zhou *et al.,* 2002; Jurica and Moore, 2003), consisting of five uridine-rich (U-rich) small nuclear RNAs (snRNAs U1, U2, U4, U5, and U6), five small nuclear RNPs (snRNPs), and a multitude of non-snRNP splicing factors, such as serine/ arginine-rich (SR) proteins (Deckert *et al.,* 2006). The spliceosome assembly which begins anew at each intron guided by consensus sequences located in the pre-mRNA is a highly ordered and dynamic reaction (Wahl *et al.,* 2009). During the course of splicing, the sequences of exon and intron have to be recognized effectively and appropriate 5′ and 3′ splice sites (5′-SS and 3′-SS) have to be chosen before the catalytic step (Wang and Burge, 2008).

Three conserved elements in introns of the pre-mRNAs that are *cis*-acting comprise of the 5′-SS with a conserved GU dinucleotide, the 3′-SS with a conserved AG dinucleotide, in addition to the branch point sequence (BPS) with a conserved UACUAAC sequence in yeast, but little conserved BPS in other higher eukaryotes located about 18–40 nt upstream of the 3′-SS (Wang and Burge, 2008). The splicing complexes help in recognizing these elements and take part in regulating the splicing reactions.

The assembly procedure of the spliceosome is exceedingly dynamic by the formation of several intermediate complexes, referred to as E, A, B, and B* (Deckert *et al.,* 2006; Will and Luhrmann, 2011). The interaction of U1 snRNP takes place with the conserved 5′-SS, resulting in the complex E or early pre-splicing complex.

At this point, the U2 snRNP is related loosely to the pre-mRNA (Das *et al.,* 2000; Deckert *et al.,* 2006). Afterward, the U2 snRNP carries out stable interaction with the BPS of the pre-mRNA, leading to the construction of the complex A or pre-spliceosome dependent on the hydrolysis of ATP (Deckert *et al.,* 2006).

As a final point, the pre-formed U4/U6/U5 tri-snRNP particle adheres to the A complex and develops the spliceosomal B complex. This includes a full set of U snRNAs in a pre-catalytic state (Deckert *et al.,* 2006; Wahl *et al.,* 2009). Following a series of

conformational as well as compositional alterations, counting the release of the U1 and U4 snRNPs, the catalytic actions of the spliceosomal B complex are activated and forms the B* complex, the so-called activated spliceosome, to execute the sequential transport of phosphodiester (Smith *et al.*, 2008; Wahl *et al.*, 2009).

A two-step mechanism catalyzes the splicing (Deckert *et al.*, 2006; Smith *et al.*, 2008). In the first step, the 5′-SS is cleaved, and the 5′ end of the intron is linked covalently to the BPS, outlining a lariat structure. During the next step of splicing, the 3′-SS is cleaved, making the intron release and ligation of the 5′ and 3′ ends of the exons takes place for the purpose of forming the mRNA (Deckert *et al.*, 2006).

Upon disassembly of the spliceosome, both the pre-mRNA splicing products and the components of the spliceosome are released finally, and the individual subunits of the spliceosome join in subsequent rounds of splicing. The composition of the spliceosomes might be comparable to that of the animal spliceosome since many components of the spliceosomes in animals have their presence in plants, signifying that the basal mechanisms in plants are similar to that of other organisms (Lorkovic *et al.*, 2000; Reddy, 2004).

The 5′ and 3′-SS in all the introns of *Arabidopsis* and rice analyzed are very similar to those of human beings, but the non-canonical splice sites, come about in only 0.7% of all splice sites, slightly lesser than the percentage found in the animals (Reddy, 2007). Moreover, the branch point sequence (CURAY) is not obvious in plants because of the difference in the position of the branch point in diverse introns, signifying that the mechanisms concerned in splice site recognition perhaps vary in these organisms (Reddy, 2007).

Significance of alternative splicing (AS) in plants

It is an indispensable post-transcriptional regulatory mechanism that can regulate gene expression, as well as extend transcriptome plasticity and proteome diversity in the eukaryotes (Stamm *et al.*, 2005). Manifold transcripts from a single gene can be generated by exon skipping, introns' retention, and/or selection of an alternative 5′ or 3′-SS (Reddy, 2007).

The events of intron retention often generate mRNAs with premature termination codons (PTCs) (Maquat, 2004; Reddy, 2007). The mRNAs with PTCs can be translated into truncated proteins, lacking a few active domains that are present in the full-length protein. These truncated proteins can contribute to the control of the quantity of functional protein that is produced, which has been demonstrated for many genes in plants that are related to development as well as disease resistance (Dinesh-Kumar and Baker, 2000; Zhang and Gassmann, 2003; Seo *et al.*, 2012). Several variants of splicing are fixed as functional AS events in order to regulate gene expression or define the functions of certain proteins in plants, though the functions of only a limited AS events have been revealed in plants so far (Wang and Brendel, 2006).

AS is a vital mechanism for regulating the function of genes and boosting the coding potential of a genome in plants (Lorkovic *et al.*, 2000; Reddy, 2007). It plays essential tasks in regulating the development of plants and tolerance to biotic as well as abiotic stresses. On the contrary, AS is regulated by development and environmental stresses also (Brett *et al.*, 2002; Palusa *et al.*, 2007; Filichkin *et al.*, 2010). AS of *Flowering Time Control Locus A* (*FCA*) results in four transcripts (α, β, γ, and δ), which are essential in the autoregulation of its expression and the

control of the floral transition (Macknight *et al.*, 1997). Prejudicing the function of SR45, a protein that is specific to plant, consequences in a splicing defect, afterward floral transition, in addition to aberrant leaf morphology phenotypes in *Arabidopsis* (Zhang and Mount, 2009; Tanabe *et al.*, 2009). AS of most SR genes is altered by abiotic stresses strongly. Alternatively spliced forms of *SR1* are regulated by high temperature (Lazar and Goodman, 2000).

Regulatory functions of alternative splicing in the circadian clock

Functions of AS in regulating the expression of the clock genes have been found out in recent times. More data in *Arabidopsis* discloses the importance of AS in the control of the clock (Wang and Ma, 2013). The clock-regulated *Protein Arginine Methyl Transferase 5* (*AtPRMT5*) gene encodes a type II protein arginine methyltransferase that catalyzes the methylation of varied substrates (Deng *et al.*, 2010). Mutations in *atprmt5* trim down the methylation of the spliceosome components, such as AtSmD1 and AtLSm4, resulting in the splicing defects in genes engaged in many biological progressions (Sanchez *et al.*, 2010; Deng *et al.*, 2010). The circadian period is stretched by *atprmt5* mutations (Hong *et al.*, 2010). Imperfections in the alternative splicing of *PRR7* and *PRR9* in *atprmt5-5* are responsible for the elongated period of the clock, first connecting AS to the clock (Sanchez *et al.*, 2010).

Two additional splicing factors, Ski-interacting protein (SKIP) and Spliceosomal Timekeeper Locus1 (STIPL1), are engaged in the regulation of the circadian clock in *Arabidopsis* (Jones *et al.*, 2012; Wang *et al.*, 2012). STIPL1 is one another splicing factor linked with the regulation of the circadian clock, which encodes a homolog of Tuftelin-Interacting Protein11 (TFIP11) in the human-beings and Ntr1p in yeast is involved in disassembly of the spliceosome (Tannukit *et al.*, 2009; Jones *et al.*, 2012). These findings imply that the splicing factors, including AtSKIP and STIPL1, are necessitated for the accurate splicing of the genes related to circadian clock and for the normal functioning of the circadian clock. Thus, autoregulation of the transcription factors by generating competitive inhibitors through alternative splicing may be a common mechanism in their expression.

AS not regulates the functions of the circadian clock or the clock-related genes only, but also is under the control of the circadian clock (Staiger and Green, 2011). About 25–33% of the protein-coding genes are regulated by the circadian clock at the entire-genome scale of *Arabidopsis* (Covington *et al.*, 2008; Hazen *et al.*, 2009). A number of other genes also demonstrate >4h phase differences between the oscillating introns and exons of the same transcriptional unit. A few genes have two splice forms- one is with but the other is without a cycling intron (Hazen *et al.*, 2009).

Other than AS, microRNA (miRNA)-mediated gene silencing is also an emerging regulatory mechanism to control the function of the circadian clock. MiRNAs are a plentiful group of endogenous, short (20–22 nt), single-stranded, non-coding RNAs that perform as post-transcriptional regulators of gene expression through sequence-specific cleavage or translational suppression of their target mRNAs in plants as well as animals (He and Hannon, 2004; Bartel, 2004). It has been recommended that each miRNA can control hundreds of target genes in humans, and > 60% of the protein-coding genes are the targets of miRNA (Friedman *et al.*, 2009). The expression of miRNAs is regulated by the circadian clock (Cheng *et al.*, 2007; Hazen *et al.*, 2009) (Fig. 1 and 2).

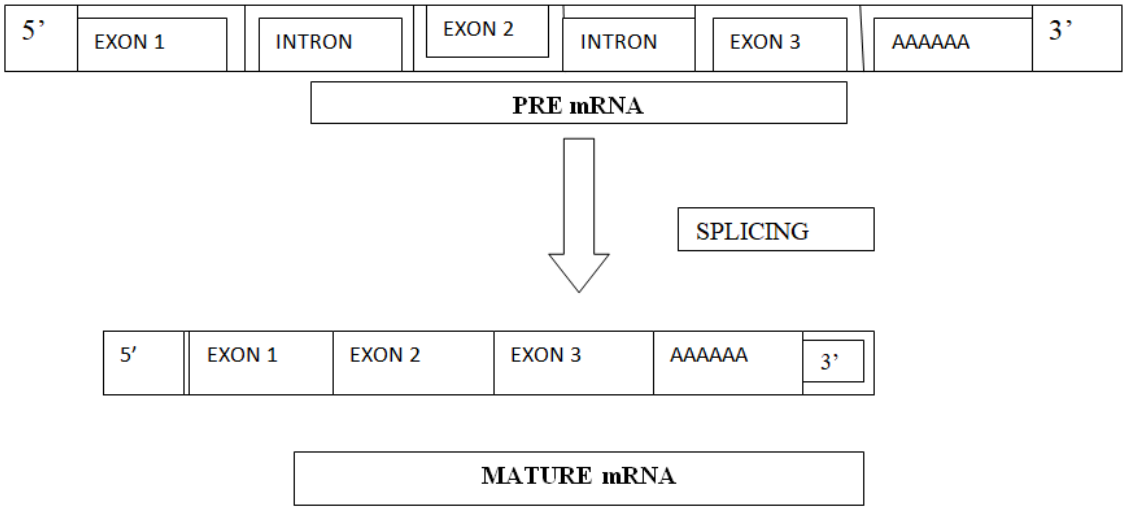

Figure.1 Mature-mRNA processing from Pre-mRNA

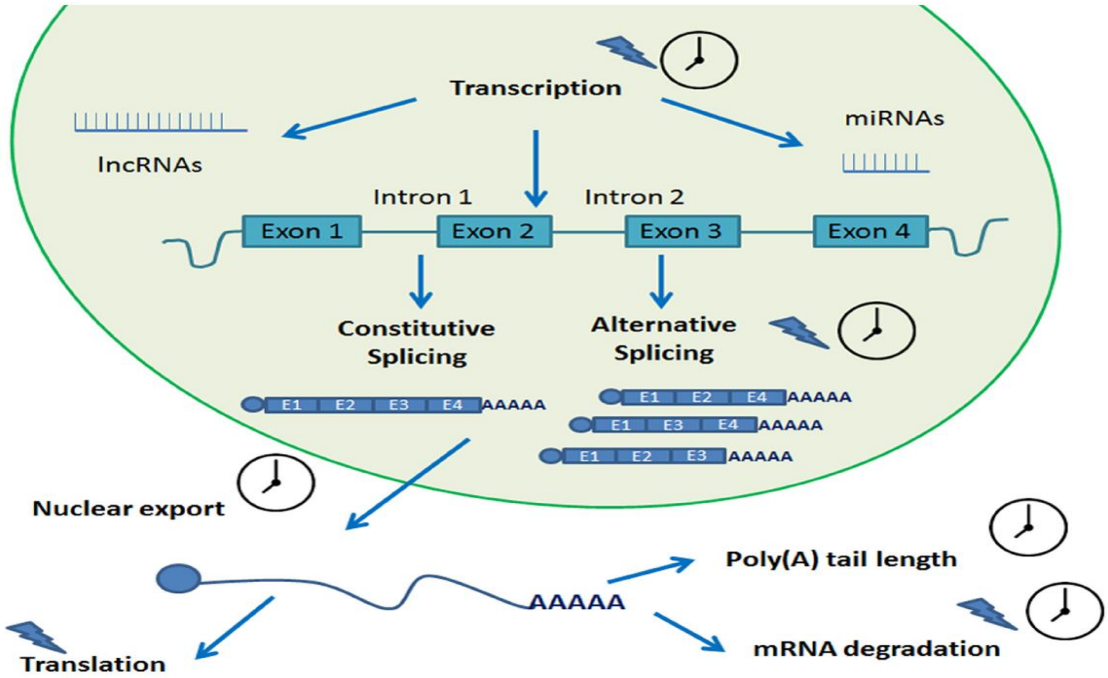

Figure.2 Post-transcriptional processes involved in circadian biology (Romanowski and Yanovsky, 2015)

A number of miRNAs controlled by the circadian clock have been recognized in *Arabidopsis* by employing whole-genome TILLING arrays, including *miR-160b*, *miR-167d*, *miR-158a*, and *miR-157a* miRNAs in *Arabidopsis* (Hazen *et al.*, 2009). In *Arabidopsis*, photoperiodic flowering control is one of the circadian clock outputs that have been revealed to be under the regulation of miRNA (Schwab *et al.*, 2005; Jung *et al.*, 2007). The core components in the photoperiodic control flowering pathway,

such as GI, COSTANS (CO), and Flowering Locus T (FT), show evidence of circadian rhythmicity (Hayama and Coupland, 2003).

To conclude we may say that the circadian clock is a vital mechanism in plants to synchronize the endogenous biological as well as biochemical procedures with the cues of the local day/night cycles. Even though AS is crucial for the normal functioning of the circadian clock, how AS regulates the circadian clock is a long way from obvious. Not only *CCA1*, but also *TOC1*, *LHY*, *PRR3*, *PRR5*, *PRR7*, *PRR9*, *GI*, *ZTL*, and other genes related to the circadian clock are subject to AS in *Arabidopsis* (Sanchez *et al.*, 2010; Seo *et al.*, 2012; James *et al.*, 2012).

However, the molecular principles of their regulation of the circadian clock are still incomprehensible. An investigation in a detailed manner into how the AS of *LHY*, *PRR7*, *PRR9*, *TOC1*, and *GI* genes plays their roles in regulating the circadian clock will elucidate the regulatory mechanisms of the circadian clock.

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