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3′ End Formation and Regulation of Eukaryotic mRNAs

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Abstract

The polyadenosine (polyA) "tail" is an essential feature at the 3′ end of nearly all eukaryotic mRNAs. This appendage has roles in many steps in the gene expression pathway and is subject to extensive regulation. Selection of alternative sites for polyA tail addition is a widely used mechanism to generate alternative mRNAs with distinct 3′UTRs that can be subject to distinct forms of posttranscriptional control. One such type of regulation includes cytoplasmic lengthening and shortening of the polyA tail, which is coupled to changes in mRNA translation and decay. Here we present a general overview of 3′ end formation in the nucleus and regulation of the polyA tail in the cytoplasm, with an emphasis on the diverse roles of 3′ end regulation in the control of gene expression in different biological systems.

Keywords

alternative polyadenylation; polyA tail control; posttranscriptional regulation

1. Introduction

Transcription by RNA polymerase II yields precursor mRNA (pre-mRNA) that undergoes multiple processing events in order to become mature mRNA that can serve as a template for translation in the cytoplasm. Pre-mRNA processing events include the addition of a 7-methyl guanosine "cap" to the pre-mRNA 5′end, the removal of introns and splicing of exons, and maturation of the mRNA 3′ end. With the exception of histone mRNAs, the 3′ ends of all mRNAs are processed by endonucleolytic cleavage and the non-templated addition of a continuous stretch of adenosines [1]. This polyadenosine (polyA) "tail," which has an average length of 250 bases in human cells, is an essential feature of mRNA with important roles in multiple steps of the mRNA life cycle. In the nucleus, 3′ end cleavage and polyadenylation of mRNA is essential for transcription termination, release of mRNA from the site of transcription, and export to the cytoplasm [2]. In the cytoplasm the polyA tail protects mRNA from degradation and enhances mRNA translation [3].

Posttranscriptional control of gene expression via factors that act on mRNA provides the cell with multiple layers to diversify and fine-tune protein output. This includes alteration of the protein-coding content of an mRNA through alternative processing of pre-mRNA into

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mRNA [4]. In addition, mature mRNAs can be subject to translational repression, localization to discrete subcellular locations, and changes in the rate of mRNA translation and decay [5, 6]. Posttranscriptional regulation is largely dependent on the binding of specific factors (RNA-binding proteins or miRNAs) to sequences in the mRNA 3′ untranslated region (3′UTR). This includes binding sites for factors that act directly or indirectly to modify the length of polyA tail present on specific mRNAs and therefore affect mRNA translation and stability. Importantly, 3′UTR regulatory sequences can be included or omitted from mature mRNA by selection of an alternative site of mRNA 3′ end formation [7]. Thus, 3′ end formation in the nucleus can impact mRNA fate in the cytoplasm.

In recent years, there has been renewed interest in the 3′end of mRNAs due to the recognition that 3′ ends are subject to extensive regulation (both in the nucleus and cytoplasm) and have important roles in cell- and tissue-specific gene expression programs. In addition, there is increasing evidence that global changes in 3′UTR length are associated with changes in cell proliferation and differentiation and that modification of polyA tail length has important roles in diverse developmental pathways [1, 7]. In this review, we provide an overview of eukaryotic mRNA 3′ end formation and regulation, with the goal of highlighting the prevalence of 3′ end regulation and the importance of the 3′UTR in posttranscriptional regulation of gene expression.

2. Cleavage and Polyadenylation of Eukaryotic mRNA

The addition of a polyA tail to the 3′ end of mRNA occurs via two tightly coupled steps. The first step is endonucleolytic cleavage of the pre-mRNA to generate a free 3′ hydroxyl that is the substrate for the second step, the non-templated addition of adenosines (polyadenylation). Cleavage and polyadenylation are dependent on multiple *cis*-acting elements and their recognition by specific RNA-binding proteins within the multi-subunit complexes that comprise the cleavage and polyadenylation machinery [8]. Here we focus on the *cis* sequences and *trans*-acting factors in mammals. For a more detailed discussion on species-specific similarities and differences in diverse organisms, we refer the reader to the following excellent reviews [9, 10].

In higher eukaryotes, >90 % of sites of cleavage and polyadenylation have a hexanucleotide polyadenylation signal (PAS) approximately 10–30 nucleotides upstream of the site of cleavage and polyadenylation (polyA site). The most common PAS hexamers used in higher eukaryotes are AAUAAA or AUUAAA, but many other variants exist, with over ten different possibilities identified in mouse and humans [8]. A second element, the downstream sequence element (DSE) is situated 10–30 bases downstream of the polyA site and consists of a more variable U-rich or UG-rich sequence. A U-rich upstream sequence element (USE) is generally present upstream of the PAS and frequently consists of UGUA. The *trans*-acting factors necessary for cleavage and polyadenylation include CPSF (cleavage and polyadenylation specificity factor), CstF (cleavage stimulatory factor), CFIm and CFIIm (mammalian cleavage factors I and II, respectively), and PAP (polyA polymerase). The 160 kilodalton (kD) subunit of CPSF (CPSF160) binds the PAS, while CPSF73 functions as the endonuclease. The position of pre-mRNA cleavage site is determined by interactions

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between CPSF and CstF, the latter of which is bound to the DSE via the 64 kD subunit of CstF (Cstf64). CFIm recognizes UGUA elements upstream of the cleavage site and is believed to regulate the interaction of CPSF with the PAS. The role of CFIIm is not well defined, although it is required along with CPSF, Cstf, CFIm, and PAP for cleavage and polyadenylation *in vitro*. PolyA-binding protein (PABP) has an important role in 3′ end formation to stabilize the interaction of CPSF to PAP during polyadenylation to ensure PAP processivity until the growing polyA tail has reached an appropriate (species-specific) length [11]. For additional details on the core factors and elements necessary for 3′ end cleavage and polyadenylation, see the following reviews [1, 7, 8, 9, 10].

3. mRNA 3’ End Formation Is Coupled to Multiple Steps in the mRNA Life Cycle

Although pre-mRNA cleavage and polyadenylation activity can be reconstituted *in vitro* using only the factors described above, 3′ end formation *in vivo* is physically and functionally coupled to multiple steps in the mRNA production pathway, including the RNA polymerase II transcription cycle [2]. Interactions between 3′ end processing factors and the transcription machinery have been described from yeast to human cells [12]. This includes, but is not limited to, the association of CPSF with transcription initiation factor IID [13] and the co-transcriptional recruitment of 3′ end processing factors to the C-terminal domain (CTD) of elongating RNA polymerase II [2]. The CTD is required for proper 3′ end formation *in vivo* [14] and can stimulate cleavage and polyadenylation when added to *in vitro* 3′ end processing assays [15]. Conversely, mutation of cleavage and polyadenylation elements results in defects in transcription termination [16]. Connections between 3′ end formation and other steps in the mRNA life cycle have also been described [1]. This includes interactions between cleavage and polyadenylation factors with pre-mRNA splicing factors, including some that have been shown to have splicing-independent functions in the regulation of polyA site utilization [17, 18]. In addition, there are links between subunits of cleavage and polyadenylation complexes and the mRNA quality control and export machinery [19]. It is believed that these interactions couple 3′ end formation to mRNA export from the nucleus and facilitate the degradation of transcripts that are not properly processed or exported. Consistent with physical and functional links between 3′ end processing factors and other proteins involved in mRNA biogenesis and gene regulation, biochemical purification of the cleavage and polyadenylation machinery from human cells revealed ~70 proteins that are associated with the “core” factors described above [20]. In addition to splicing factors and components of the transcription machinery, this ~1 megadalton complex contains a number of unexpected proteins including translation factors suggesting that 3′ end formation of mRNA may be coupled to other regulatory events in the cell.

4. Cytoplasmic Regulation of mRNA 3’ Ends

The polyA tail has an important role in mRNA translation and stability [21]. The interaction of PABP (bound to the polyA tail) with the translation initiation factors (bound to the mRNA 5′ cap) forms a “closed loop” or “circular” mRNA that facilitates translation and protects

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mRNA from degradation [22]. The formation and stability of this loop is believed to be dependent on the length of the polyA tail [3]. In general, shortening of the tail polyA results in reduced PABP binding and lower levels of translation, whereas polyA tail lengthening is associated with higher translation. A number of posttranscriptional regulatory factors have been described that control the translation of their mRNA targets by directly or indirectly modifying polyA tail length. For example, PUF family proteins (present in genomes from yeast to humans) recognize specific 3′UTR sequences to recruit deadenylases and repress translation [23]. Similarly, AU-rich elements (AREs, classically defined as AUUUA, although other variants are known to exist) comprise a class of posttranscriptional regulatory sequences in 3′UTRs that are bound by ARE-binding proteins that recruit deadenylases such as polyA ribonuclease (PARN) or the CCR4-NOT complex [24].

Although deadenylation can be coupled to mRNA decay, in some instances, deadenylation is associated with translational repression and mRNA stabilization [5]. Such regulation is believed to be essential for the proper control of mRNAs whose translation must be restricted to discrete subcellular locations and/or activated in response to specific intra- or extracellular cues. Cytoplasmic lengthening of the polyA tail promotes the translation of specific mRNAs and has been shown to be dependent on cytoplasmic polyadenylation elements (CPEs) in the 3′UTR [3]. CPEs are typically (but not limited to) UUUUAU or UUUUAAU and are bound by CPE-binding proteins (CPEBs). Interestingly, CPEBs can have dual roles in polyA tail length regulation. Depending on the location and number of CPEs in a 3′UTR, as well as the posttranslational phosphorylation status of CPEBs, CPEBs can positively or negatively impact translation by recruiting translational regulators, polyA polymerases such as Gld-2 to lengthen the polyA tail, or deadenylases such as PARN to shorten the polyA tail [25]. Such dual control of polyA tail length by the same factor binding to the same element(s) highlights the difficulty in predicting roles for RNA-binding proteins based solely on the presence of their cognate binding elements and the importance of using biochemical approaches to monitor protein-RNA interactions, posttranslational modifications, and polyA tail length.

5. Fine-Tuning Gene Expression Through Alternative Polyadenylation

Bioinformatic analyses of ESTs, and more recently, global RNA profiling approaches, have revealed that the majority of human genes (>80 %) yield multiple mRNA isoforms with alternative 3′UTRs due to differences in the position of 3′ end cleavage and polyadenylation [1, 7]. Since posttranscriptional regulatory sequences are contained within 3′UTRs, alternatively polyadenylated mRNA variants generated from the same gene are likely to be bound by different combinations of *trans*-acting factors (proteins and miRNAs) that can affect mRNA localization, translation, stability, and decay. Thus changes in the position of cleavage and polyadenylation have the potential to significantly impact downstream events in the life cycle of the mRNA by including or excluding posttranscriptional regulatory sequences in the mRNA's 3′UTR [26].

The most common type of alternative polyadenylation is that in which multiple polyA sites are arranged in tandem in the same 3′terminal exon [1]. In such cases, selection of an alternative site for cleavage and polyadenylation alters the 3′UTR sequence with no impact

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on protein-coding sequence. An excellent example of how such regulation can impact gene expression (particularly mRNA localization and translation) comes from the study of the mRNA encoding brain-derived neurotrophic factor (BDNF). BDNF is an important signaling molecule in the brain implicated in neuronal survival, circuit development, and synaptic plasticity and through these functions is also genetically linked to neurological and psychiatric disorders. Importantly, neurons produce distinct forms of BDNF mRNA [27]. BDNF mRNA generated using a proximal polyA site (shorter 3′UTR) is not localized and is translated constitutively. In contrast, selection of a distal polyA site includes 3′UTR sequences that confer localization of BDNF mRNA to dendrites. Additionally, the long 3′UTR isoform of BDNF is not translated normally, but is induced upon signaling. Thus, cell-specific differences in the relative amounts of long and short 3′UTR isoforms of BDNF may confer different levels of BDNF responsiveness in neurons.

A second class of alternative polyadenylation events includes changes in polyA site selection that are associated with alternative splicing events and therefore have the potential to change both coding potential and 3′UTR sequence. A classic example of this type of regulation is the alternative processing of IgM pre-mRNA that is associated with the switch from a membrane-bound form of IgM (which acts as a receptor on B-cells) to a secreted form of IgM that can perform the various functions of soluble immunoglobulins [28]. In resting B-cells, a distal polyA site is selected that gives rise to an mRNA bearing sequences that encode IgM with a C-terminal membrane association domain. In active B-cells, a proximal polyA site is chosen that causes loss of the membrane association motifs and thus generates a secreted form of IgM.

Alternative processing of pre-mRNA encoding the transcription factor CREM-tau represents an example of the ability of alternative polyadenylation to modulate gene expression at multiple levels. CREM is a transcription factor critical for proper male germ cell development (spermatogenesis). CREM pre-mRNA is subject to complex RNA processing, producing various isoforms of the transcription factor with various activities ranging from repressor to activator [29, 30]. In early stages of spermatogenesis, the CREM gene yields a transcription factor that functions as a repressor. However, at a specific point in spermatogenesis, alternative promoter usage and alternative splicing generate CREM mRNA isoforms that encode a protein with transcriptional activation activity. This switch is coupled with selection of a polyA site that generates a short 3′UTR that lacks instability elements, and thus becomes stabilized, and thus leads to a large accumulation of CREM-tau activator. This switch is critical for activator activity of CREM-tau and proper progression through male germ cell development.

6. Global Programs of 3’ End Regulation

It is becoming increasingly apparent that many developmental processes exhibit distinct signatures of alternatively polyadenylated mRNAs and that global reprogramming of 3′UTRs has important functions in cell proliferation, differentiation, and tissue development (for reviews, *see* refs. 1, 7). Early embryogenesis highlights the intersection of regulated 3′ end formation and polyA tail length control [31, 32, 33]. Very early after fertilization of oocytes, transcription is silent, and maternally derived mRNAs with long 3′UTRs containing

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CPEs are positively regulated by CPEBs to drive early embryogenesis. Upon transcriptional activation of the zygotic genome, factors are expressed that bind to maternal mRNAs 3′UTRs and mediate their degradation. In addition, the newly expressed genes generally have shorter 3′UTRs and thus lack these negative regulatory sites. In general, these genes are involved in the rapid cell divisions in the early embryo.

A second example which illustrates how global reprogramming of 3′UTRs could be driving cellular processes is provided by the study of T-cell activation [34]. In quiescent T-cells, genes required for activation express mRNAs with long 3′UTRs, many of which have sequences recognized by miRNAs; thus these mRNAs are poorly translated and readily degraded. While the protein products are being made at low levels, the mRNAs encoding activation factors are still being produced, resulting in a T-cell "primed" for rapid activation. Upon stimulation of T-cells, alternative polyA site selection results in a general shortening of 3′UTRs in important regulatory genes. This 3′UTR shortening removes miRNA binding sites that negatively regulate translation and mRNA abundance, thus allowing higher levels of expression of the encoded proteins. Interestingly, global analyses have revealed tissue-specific biases in 3′UTR length, with the most notable examples being brain and testis that generally express mRNAs with long and short 3′UTRs, respectively [35, 36, 37, 38]. The functional significance of these tissue-specific differences remains unclear.

While it is clear that alternative polyadenylation and cytoplasmic control of polyA tail length are widely used mechanisms of posttranscriptional gene regulation [3, 26], our understanding of how these processes are controlled remains limited. In some cases, tissue-specific auxiliary factors are believed to control the access of the polyA machinery to alternative polyA sites. For example, the neuron-specific RNA-binding protein Nova2 can bind to sequences that overlap with the PAS or DSE of proximal polyA sites to repress 3′ end formation presumably by competition with CPSF and CstF, respectively [39]. In contrast, Nova2 binding to sequences adjacent to (but not overlapping with) core cleavage and polyadenylation sequences is associated with Nova2-dependent selection of alternative polyA sites, possibly through antagonizing negative auxiliary factors. Modulation of core components of the cleavage and polyadenylation machinery is also believed to be a mechanism of polyA site regulation. For example, in resting B-cells, lower levels of CstF are thought to be one factor favoring distal polyA site usage and thus expression of membrane-bound IgM (*see* example above). Activation of B-cells is accompanied by increased expression of CstF, which is thought to be one factor favoring proximal polyA site usage, and thus production of secreted IgM [28]. While more recent studies have shown that regulation of this processing switch involves additional *cis*-acting sequences and *trans*-acting factors [40], it is clear that regulation by CstF levels is part of the picture. The coupling of 3′ end processing and regulation to multiple steps in the mRNA life cycle and the multifunctionality of RNA-binding proteins suggests that 3′ ends are most likely subject to combinatorial control by a number of factors that act at multiple steps in the biogenesis and metabolism of mRNA. Interestingly, a recent study demonstrated a role for PABP in regulation of alternative polyadenylation [41], while a second report found evidence that CPEB can regulate alternative splicing and polyadenylation in addition to regulating polyA tail length [42]; thus these proteins can coordinate multiple layers of posttranscriptional gene regulation.

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7. Conclusion

The examples described in this chapter were selected to illustrate the significance of the mRNA 3′ end (both the position of polyadenylation and length of polyA tail) in posttranscriptional control of gene expression. Moving forward, a better understanding of how networks of mRNAs are co-regulated at their 3′ends will provide new insights into mechanisms of gene regulation in different cells and stages of development. New global profiling methods (e.g., HITS-CLIP and bioinformatic analyses) combined with traditional *in vitro* biochemical assays provide a powerful approach to explore the roles of putative regulatory factors in polyA site regulation and polyA tail length control [43]. Considering the impact of the mRNA 3′ end on gene output, the use of gene expression profiling approaches that do not incorporate polyA site information is likely to yield an incomplete picture of the mRNA landscape of the cell and preclude the identification of 3′ end regulatory events that may impact gene expression pathways. Fortunately, a number of new deep sequencing methods have been developed in recent years that are capable of generating comprehensive measurements of alternative 3′UTR expression in a global manner [1]. These tools have shown that alternative 3′ end processing is a widespread occurrence with central roles in many important processes, such as cellular proliferation, differentiation, T-cell activation, and development of many tissues [26]. A major challenge for the future will be to move beyond global descriptions of regulated mRNA 3′ ends and towards a better understanding of the functional significance of 3′ end regulation in different cellular contexts. Combining global profiling studies of polyA sites with analyses of mRNA polyA tail length, translation, stability, and localization will help better understand the impact of 3′ end regulation on the expression of networks of genes important for different biological processes.

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