Post-transcriptional regulation of early embryogenesis

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Abstract

Gene expression is controlled by diverse mechanisms before, during, and after transcription. Chromatin modification factors as well as transcriptional repressors, silencers, and enhancers all feed into how eukaryotes transcribe RNA in the nucleus. However, there is increasing evidence that post-transcriptional regulation of gene expression is as widespread as transcriptional control if not more so. Studies of specific transcripts in oocytes and embryos are at the core of our mechanistic understanding of many post-transcriptional events. Coupled with genome-wide and large-scale experimental approaches, research is bringing to light how these regulatory events function independently and in concert to regulate protein expression.

Introduction

Regulation of protein expression is orchestrated through the interaction of trans-acting factors with *cis*-regulatory elements. Different factors are targeted to specific sequence regions or secondary structures in the transcript to promote different outcomes, including initiation of translation and degradation. Key regulatory steps in generating differential protein expression include the co-transcriptional events of pre-messenger RNA (mRNA) splicing, capping of the mRNA 5′ end, and polyadenylation. Post-transcriptional control can be exerted through de-capping, deadenylation, and cytoplasmic polyadenylation. Additionally, mRNAs in the cytoplasm will often undergo transport, storage, and quality control, which influence the location and level of protein expression [1]. All of these processes can be modulated by interactions with RNA-binding proteins and non-coding RNAs.

For over half a century, research has focused on how these processes function individually and synchronously to control when and where proteins are made. Biochemical experiments using oocytes, embryos, yeast, and cultured cells first identified the factors involved and established the role of proteins in post-transcriptional regulation. Diligent exploration of individual RNAs then enabled detailed models to be built for the different mechanisms of regulation. A burst in genome-wide and big-data approaches is now challenging previous assumptions and is uncovering levels of complexity in post-transcriptional control of protein expression.
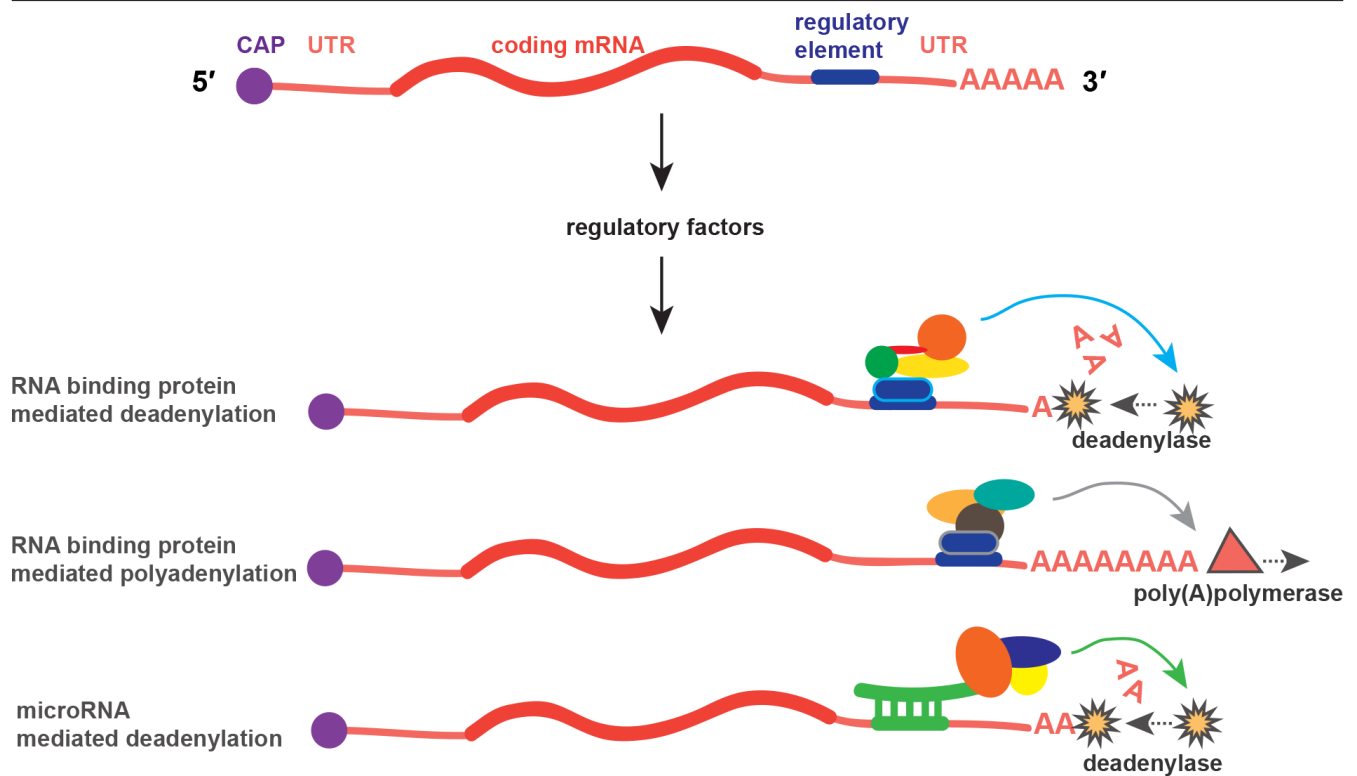
Based on recent breakthroughs, this article will discuss how new types of data are reshaping our understanding of post-transcriptional regulation in embryogenesis, with a focus on poly(A) tails and the 3′ untranslated region (UTR). I will consider outstanding questions such as the following: how do length, inclusion, and exclusion of the 3′ UTR influence mRNA fate? Does poly(A) tail length directly influence translational outcomes? How is the balance between polyadenylation and deadenylation managed in the cytoplasm? When and at what level do microRNAs (miRNAs) function through mRNA decay, repression, and deadenylation? Can one factor influence multiple aspects of post-transcriptional regulation? The priority of resolving these and other queries is bolstered by increasing data linking human disease progression and severity to transcript regulation [2–4]. In the future, unraveling the nuances and intricacies of post-transcriptional regulation will once again require mechanistic analyses of individual transcripts. The scope of this article is limited, and the aim is to provide a glimpse of the emerging questions. Any oversights are unintentional as the field is historically rich and rapidly expanding.

The ending matters: poly(A) tails

In the early 1970s, fractionation experiments on mammalian cells isolated polysome-associated mRNAs. An intriguing observation was made when these mRNAs were cut with RNases specific to C and U as well as G; there was a long, resistant fraction. This fraction was proposed to consist of a poly(A) sequence not encoded by the DNA template. This was confirmed upon the discovery of poly (A) polymerase (reviewed in [5]). During the same period, researchers showed that poly(A) elongation commonly takes place in oogenesis, providing an important biological model [6]. By the end of the 1980s, experiments in frog and mouse oocytes showed that regions of the 3′ UTR of mRNA had the capacity to confer polyadenylation and initiate translation. This was somewhat surprising as the convention at the time was that the 5′ UTR regulated translation. It was quickly established, in both vertebrates and invertebrates, that specific mRNAs were dependent on lengthened poly(A) tails for translation and that deadenylation, in some cases, directly resulted in translational repression (Figure 1). Moreover, *Caenorhabditis elegans* and marine invertebrates displayed systematic changes in poly(A) length during development [7].

In many organisms, there is a delay after fertilization before the zygotic genome is transcribed, and this is why maternal mRNAs and post-transcriptional regulation are so important. The typical default state of the mRNA in oocytes is translationally repressed. This remains the case until inhibitors are removed or outcompeted by other factors for elements in mRNA UTR. Interaction between the 5′ and 3′ UTR-associated proteins often circularizes the mRNA, thus preventing the small ribosomal subunit from positioning on the transcript and initiating translation. The oocyte and early embryo of *Drosophila* have been the focus of decades of research on mRNA translational control [8,9]. With a broad-scale approach taken by many researchers in the field, gene expression was recently measured by microarray and demonstrated that a specific poly(A) polymerase is required for the elongation of thousands of mRNAs at the transition from oocyte to embryo [10]. A post-fertilization wave of gene expression due to maternal mRNA polyadenylation is also observed in frogs by high-resolution profiling of gene expression [11]. These data are consistent with other work [12] and suggest that cytoplasmic polyadenylation is a general regulator of translation at this developmental transition.

Figure 1. Modification of poly(A) tails

The binding of trans-acting factors to the regulatory element in the 3′ UTR can result in recruitment of different downstream proteins and enzymes. Changes in the poly(A) tail length are important for translation and mRNA stability. Abbreviations: mRNA, messenger RNA; UTR, untranslated region.

Once maternal mRNAs have been translated, they are degraded and the onset of zygotic transcription, known as the maternal-to-zygotic transition, follows. How these mRNAs are cleared was tested by transcriptome-wide analysis in oocytes, one-cell embryos, and two-cell embryos of *C. elegans* and revealed that clearance of mRNA following fertilization is mediated by poly(C) motifs in the 3′ UTR of the mRNA [13]. It will be important to test what, if any, other components are also required at this stage and whether this mechanism of clearance is unique to worms. Both the identification and authenticity of the *C. elegans* 3′ UTR have been areas of debate. Differing methods resulted in contrasting size, site specificity, and the number of 3′ UTRs reported [14,15]. The evidence seems clear now that worm 3′ UTRs are much shorter than those of mammals (approximately one sixth) but are twice as dense in conserved miRNA sites [14]. As work in worms moves forward, it has important links to the evolution of the genome architecture and is generating new techniques for studying post-transcriptional gene regulation.

The same method used to accurately map poly(A) regions in *C. elegans* was used in a vertebrate model, zebrafish, to show that mRNAs experience cleavage and polyadenylation through development [16]. A large wave of cytoplasmic polyadenylation is detected 2 hours post-fertilization, but why and exactly how this event takes place remain unclear [16]. One possible model is that transcripts could be sites of competitive de-adenylation and re-adenylation, resulting in differential expression or decay. In mouse development, mRNAs with short 3′ UTRs are preferentially targeted for degradation [17], demonstrating again the importance of regulating the length in the 3′ UTR.

It is clear that translational regulation of mRNAs is essential in early animal development and is a highly conserved mechanism for temporal control of gene expression. Although the presence of a non-templated poly(A) tail on mRNA is presumed to lead to translation, a recent advancement in globally and accurately measuring the length of poly(A) tails has led to new models for the outcome of polyadenylation. In a survey of the individual length of millions of RNAs from different plants, animals, and developmental stages therein, the results show that on large-scale poly(A) tail length and translation are not always coupled [12]. As predicted, frog and zebrafish embryos displayed a strong correlation between poly(A) tail length and translation prior to gastrulation but, importantly, not after. Samples from non-embryonic tissue show no correlation between tail length and translation [12]. This work challenges the assumption that poly(A) elongation is synonymous with translation.
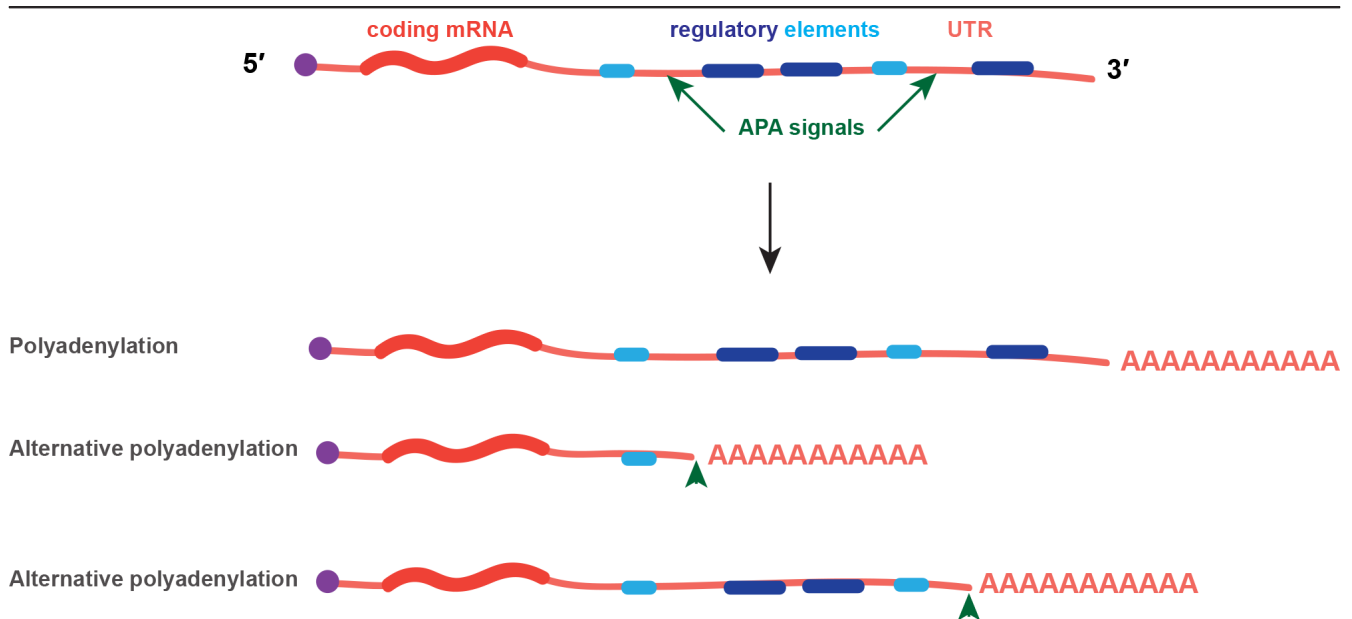
As the understanding and importance of post-transcriptional regulation, especially of the poly(A) tail and UTR, have expanded, research has increased in depth as well as breadth. Examples of ongoing broad research in the field include the following: work on the maternal 3′ UTR of Atlantic cod seeking to increase egg viability [18], an ongoing debate in plants on how factors that control poly(A) site choice are regulated [19], and testing of therapeutics that alter mRNA half-life through manipulation of UTRs, which could potentially block the progression of breast cancer, bipolar affective disorder, hereditary thrombocythemia, fragile X syndrome, and Alzheimer's disease [2,3].

A spanner in the works: alternative polyadenylation

An emerging mechanism adding a level of complexity to the transcriptome is alternative polyadenylation (APA) (Figure 2). This is a general term inclusive of multiple classes of events that through cleavage and polyadenylation generate mRNA isoforms with different 3′ UTRs. In addition to changes in the 3′ UTR, less common classes of APA involve alternation of introns and exons [20]. The full implication of APA is unclear; however, more targeted mechanistic analysis in the future will be key to understanding this process and its outcomes. Experimental observations that could lead to further breakthroughs include work showing that ubiquitously transcribed genes in human cells gain tissue specificity through APA [4] and that the RNA localization of brain-derived neurotrophic factor and CaMKIIα both involve APA [21]. It is exciting to hypothesize that APA could be involved in mRNA localization in oocytes and embryos as well [8,9]. Moreover, during cell proliferation, APA has been shown to play a role in generating mRNAs with shorter 3′ UTRs and in turn less miRNA target sites, likely conferring unique regulation [22].

A direct link to embryogenesis has been shown in the mouse model. As a result of APA, during the progression of development, mRNAs with longer 3′ UTRs are detected [23]. With longer 3′ UTRs and more AU-rich sequences, it is suggested that mRNAs later in development are likely to undergo more extensive post-transcriptional regulation [23]. There is also evidence from zebrafish that high levels of APA occur throughout development [16] and in *Drosophila* where additional regulation is conferred in neural tissue by the inclusion of more repressor-binding sites in the 3′ UTR of mRNA [24]. Deep sequencing of the transcriptome has been paramount in identifying and annotating APA regulation in varied conditions, but the core biological mechanism remains elusive. Despite these examples, few transcripts show stability changes in association with APA. Therefore, questions remain as to

Figure 2. Alternative polyadenylation

Alternative polyadenylation can change the length of the mRNA 3' UTR resulting in the inclusion or exclusion of regulatory elements. This results in the binding of different trans-acting factors, including proteins and miRNAs, which confer specific post-transcriptional regulation. Abbreviations: APA, alternative polyadenylation; miRNA, microRNA; mRNA, messenger RNA; UTR, untranslated region.

what the role of APA is with respect to localization and translational efficiency. However, over half of human genes are predicted to generate variable 3' UTRs this way [4], raising the possibility of major medical implications through manipulation of APA function.

Therefore, the ability to shorten or lengthen the 3' UTR by APA could lead to the inclusion or exclusion of different types of regulatory sequences in the mRNA. In this way, regulation of APA might produce different classes of transcripts with different regulatory potential. For example, a neuronal isoform with an extended 3' UTR might contain mRNA stability elements, whereas in a different cell type, polyadenylation at an upstream site would generate an isoform that has a short half-life. Given the many different regulatory sequences present in 3' UTRs, including cytoplasmic polyadenylation elements, (A+U)-rich elements, and RNA localization elements [8,25,26], APA could easily and directly alter the fate of the mRNA.

Sweat the small stuff: microRNAs

In addition to proteins binding the 3' UTR, non-coding RNAs also recognize and bind target sequences. Individual miRNAs have the capacity to downregulate many different target mRNAs and in some examples promote clearance of maternal mRNAs in embryogenesis [27–30] (Figure 1). To test for the global impact of miRNAs in

protein production, quantitative mass spectrometry on cultured cells was used to assay changes in protein levels before and after the addition of miRNAs [31]. The results show that destabilization was the major cause of repression for the highly repressed mRNA. This work also led to the proposal that miRNAs act to make fine-tuning adjustments on protein levels [31]. However, to what degree are miRNAs acting by repressing translation or destabilizing mRNA? Correlation of ribosomal profiling data with measured mRNA levels tested this question in mammalian cells [32]. This work showed that lowered mRNA levels account for a majority of the change in protein abundance. Ribosomal profiling was also used to decipher how miRNAs regulate gene expression in zebrafish embryos [33]. It was shown, by testing the ribosome occupancy on transcripts in different conditions, that the specific miRNA tested functioned first to regulate initiation of translation and then in decay of the target mRNA [33]. These examples highlight a level of complexity to the system where one factor can influence multiple aspects of post-transcriptional regulation. Moreover, miRNAs have been shown to function by different post-transcriptional mechanisms of regulation depending on the stage of development. In pre-gastrulation zebrafish embryos, miRNAs function to reduce poly(A) tail length, resulting in translational inefficiency, and after this stage miRNAs are thought to regulate mRNA though destabilization [12]. Although a full discussion is

outside the scope of this article [34–37], unraveling precisely how, and to what extent, non-coding RNAs regulate mRNA is crucial when considering their prevalence.

Onward and upward: the future

Given all of the possible layers of regulation in a 3′ UTR and the mechanisms of generating the UTR, post-transcriptional regulation is a complex and compelling area of research. The genome era introduced new approaches to longstanding questions in post-transcriptional control, many of which began in yeast. For example, microarray-based measurements correlated the length of mRNA poly(A) tail lengths and the binding of a key protein with general translation in budding yeast [38]. Also, ribosomal profiling enabled genome-wide analysis of translation and showed substantial translational control in response to environmental stress and total protein levels [39]. Owing to conserved mechanisms, research in yeast is important for building the foundation for further understanding in mRNA regulation in embryogenesis.

One intriguing mechanism of regulating gene expression from yeast shows a connection between synthesis and decay of mRNA through shuttling of mRNA decay factors back into the nucleus [40,41]. Whether similar factors are found in other systems to have a dual role is not clear, but this leads to the exciting hypothesis that feedback from the cytoplasm is regulating events in the nucleus. A second possible research area is comparative dynamic transcriptome analysis, which can monitor mRNA levels without perturbing metabolism [42]. In specific yeast strains tested, it was shown that when mRNA degradation rates are altered, the cell's synthesis rate was reduced as well, resulting in buffering of the system. This work again suggests a level of interconnected surveillance for registering mRNA levels in the cell to take subsequent action and could to be applied outside of yeast.

The application of approaches from different systems, as well as establishing new protocols for testing changes in 3′ UTR composition, is important to decipher the molecular mechanism of these regulatory processes. However, establishing how different mechanisms are coordinated and how they relate to one another will be key to fully understanding post-transcriptional regulation not only in the early embryo but in all cells.

Conclusions

Questions about post-transcriptional regulation are being asked more rapidly than answered. However, as demonstrated by a global comparison of mRNA and protein abundance in different nematode species, separated by 30 million years of evolution, these mechanisms

are important and widespread [43]. Genomic techniques are uncovering exciting levels of control previously unknown and are important to the progression of the field. Alongside this work, classic biochemical and genetic approaches are essential to fully understanding mechanisms of mRNA post-transcriptional regulation.

Abbreviations

APA, alternative polyadenylation; miRNA, microRNA; mRNA, messenger RNA; UTR, untranslated region.

Disclosures

The author declares that he has no competing interests.

Acknowledgments

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