Trends in Genetics

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Spotlight

Start of life controlled by poly(A) tail-mediated remodeling

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Understanding a remarkable event at the start of life, the oocyte-to-embryo transition (OET), has remained elusive, especially in humans. Using newly developed techniques, Liu *et al.* showed that human maternal mRNAs undergo global poly(A) tail-mediated remodeling during OET, identified the enzymes involved, and demonstrated the essentiality of remodeling for embryo cleavage.

Mature mammalian eggs are arrested in meiosis II (MII) and are transcriptionally silent. Upon fertilization, the arrested MII eggs enter the mitotic cell cycle, and the chromatin from the highly differentiated sperm and egg cells both go through rapid remodeling so that they can be reprogrammed into a totipotent state [1]. Concurrent with this reprogramming is the degradation of the maternal mRNAs and the activation of a large group of zygotic genes important for embryonic development [2] (Figure 1). These events following fertilization are collectively termed the OET, and they are some of the most important events at the beginning of mammalian life. Because transcription does not take place until zygotic genome activation (ZGA), many events occurring during OET are regulated post-transcriptionally through maternal mRNAs [3].

One of the post-transcriptional events is the addition of a poly(A) tail to the 3′-end of mRNAs, which is known to play important roles in regulating mRNA stability and translation [3]. After the initial addition of the tail, it is subject to further remodeling, and this further remodeling has been reported to be important for OET in several species including *Drosophila*, *Danio rerio*, and *Xenopus*. With the development of methods that allow analysis of transcriptome-wide poly(A) tails, dynamic changes of mRNA poly(A) tails during OET in these species have been revealed [4,5]. However, these methods require a large amount of input mRNAs for poly(A) profiling [4,5], and thus are not applicable to studies in mammals where there is only a limited supply of oocytes and embryos. Thus, the transcriptome-wide poly(A) tail landscape during mammalian OET remains largely unknown.

Using their newly developed more sensitive methods, named poly(A) inclusive RNA isoform sequencing (PAIso-seq [6] and PAIso-seq2 [7]), that allow poly(A) tail profiling using as little as a single oocyte or embryo, Liu *et al.* [8] comprehensively profiled the transcriptome-wide poly(A) tails in fully grown and mature human oocytes, as well as in different stages of preimplantation embryos. Their study revealed that the poly(A) tails of human maternal mRNAs undergo global remodeling during OET (Figure 1). The main findings include: (i) ~60% of maternal mRNAs are present as polyadenylated degradation intermediates (PDIs) in one-, two-, and four-cell embryos before ZGA; (ii) the PDIs have partially degraded 3′-UTRs as well as remodeled poly(A) tails that are different from those found in the mature oocytes; and (iii) compared to those in MII oocytes, the remodeled poly(A) tails are enriched in non-A residues (U, G, and C) and have a particularly high percentage of U residues.

The authors further identified the enzymes involved in poly(A) remodeling and provided evidence suggesting that the PDIs are likely generated by re-polyadenylation of partially degraded maternal mRNAs. First, the PDIs contained shorter 3′-UTRs and some had polyadenylation sites within the coding sequences (CDSs). Second, knockdown of BTG4, a core component of the deadenylase complex, significantly decreased the PDI level, which is consistent with the notion that deadenylation is involved in generating substrates for readenylation. Third, knockdown of TUT4 and TUT7, two terminal uridylyl transferases responsible for U residue incorporation into the poly(A) tail, significantly decreased the long consecutive internal U in PDIs. Finally, knockdown of TENT4A and TENT4B, two enzymes responsible for G incorporation, significantly reduced the internal G levels in the mRNAs of the human one-cell embryo, confirming that the incorporation of internal G residues in human embryos is also mediated by TENT4A and TENT4B, and may help to stabilize the re-polyadenylated mRNAs.

To begin to understand the biological significance of poly(A) remodeling during OET, particularly re-polyadenylation, the authors treated the embryos with 3′-deoxyadenosine (3′-dA) immediately after fertilization to block re-polyadenylation. The 3′-dA can be converted to 3′-dATP in cells, whose incorporation into poly(A) tails can prevent further cytoplasmic polyadenylation. This treatment efficiently blocked the embryos from developing. PAIso-seq2 analysis of the arrested one-cell embryos indicated that they have significantly decreased PDI levels as well as internal non-A residues in poly(A) tails. Furthermore, the decrease of 3′-end U residues due to their conversion to internal U residues during re-polyadenylation was also blocked. Collectively, these results support the notion that maternal mRNA re-polyadenylation during OET is essential for the development of early human embryos.

The work by Liu *et al.* is a breakthrough study on human OET because it not only provides a comprehensive, dynamic picture of human maternal mRNA poly(A) tails during OET, which can serve as a resource for integrated analysis, but, more

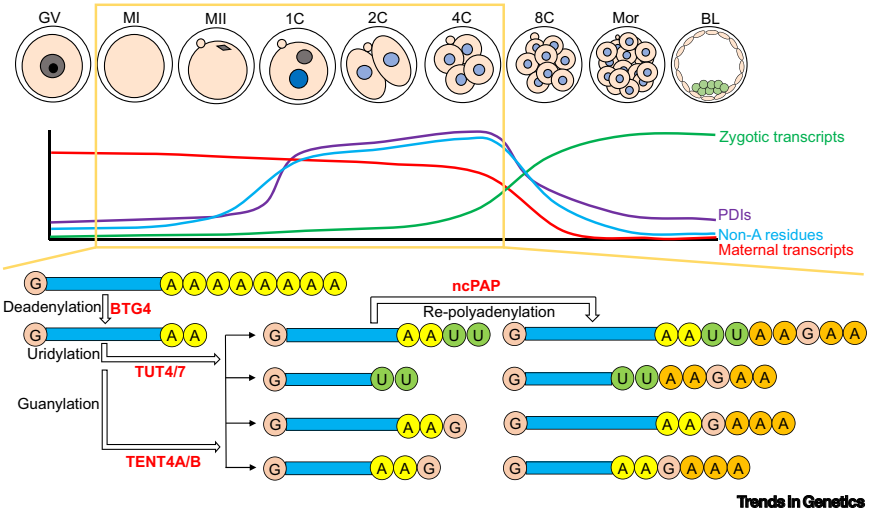

Figure 1. Summary of poly(A) tail remodeling dynamics during the human oocyte-to-embryo transition. After fertilization, maternal transcripts are gradually degraded (red), and zygotic genome activation occurs after the late four-cell (4C) stage (green). Polyadenylated degradation intermediates (PDIs; purple) and non-A (U, C, and G) residues (blue) increase to peak at the one-cell (1C) to 4C stages. During this time-window, BTG4 mediates the deadenylation of maternal mRNAs, which are then subject to degradation by exonucleases. Deadenylated or partially degraded maternal mRNAs will be uridylated by TUT4/7 or guanylated by TENT4A/4B. In addition, re-polyadenylation can be processed by non-canonical poly(A) polymerase (ncPAP) to generate maternal mRNAs with PDIs and poly(A) tails with non-A residues. Abbreviations: BL, blastocyst; GV, germinal vesicle; MI, metaphase I; MII, metaphase II; Mor, morula.

importantly, it also revealed a previously unknown phenomenon: the generation of partially degraded mRNA transcripts during oocyte maturation, which serve as substrates for re-polyadenylation. Like any other new discovery, the study raises more questions that warrant further investigation. For example, is this phenomenon unique to humans or is it conserved in other mammals and non-mammalian species? Why is this deadenylation–readenylation process needed, and why does this phenomenon only take place in some (60%) of maternal mRNAs? What is the function of this poly(A) remodeling, and is it related to mRNA stability and/or translational efficiency? What factors protect the PDIs from further degradation? What is the function of the non-A residues incorporated during this process, and are there specific factors that recognize the modified poly(A) tails? The improvement of technologies has allowed transcriptome-wide low-input ribosome profiling during mouse and human OET [9,10]. An integrative analysis of poly(A) tail remodeling and the translational efficiency may reveal some links between the two events. Given how fast the field has progressed in the past several years, we anticipate that many of the questions raised above will be solved in the coming years.

Declaration of interests

The authors declare no conflicts of interest.

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