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Review

Cytoplasmic mRNA turnover and ageing

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ABSTRACT

Messenger RNA (mRNA) turnover that determines the lifetime of cytoplasmic mRNAs is a means to control gene expression under both normal and stress conditions, whereas its impact on ageing and age-related disorders has just become evident. Gene expression control is achieved at the level of the mRNA clearance as well as mRNA stability and accessibility to other molecules. All these processes are regulated by *cis*-acting motifs and *trans*-acting factors that determine the rates of translation and degradation of transcripts. Specific messenger RNA granules that harbor the mRNA decay machinery or various factors, involved in translational repression and transient storage of mRNAs, are also part of the mRNA fate regulation. Their assembly and function can be modulated to promote stress resistance to adverse conditions and over time affect the ageing process and the lifespan of the organism. Here, we provide insights into the complex relationships of ageing modulators and mRNA turnover mechanisms.

1. Introduction

As ageing advances, a progressive decline in the ability of cells to preserve a functional proteome occurs, leading to widespread protein aggregation over time (Koga et al., 2011). Also, defects in cellular protein quality control mechanisms may constitute a common basis for the abnormal accumulation of proteins in age-dependent neurodegenerative disorders (Vilchez et al., 2014). In a physiological context, several levels of protein quality control exist, starting from the regulation of transcription and translation to the maintenance of proteome through clearance and repair mechanisms. Post-transcriptional control of gene expression at the level of messenger RNA (mRNA) translation and degradation is fundamental for determining protein levels, given that mRNA half-life ranges from a few minutes to many hours. Post-transcriptional mechanisms can regulate not only the amount but also the time and place of mRNAs that are translated into new proteins (Sonenberg and Hinnebusch, 2009; Spriggs et al., 2010). This regulation is vital for an organism to develop, grow and survive under both physiological and stress conditions. Furthermore, it has been shown across species that major signaling pathways that control the translation process can promote longevity and prevent age-related diseases. In this frame, cellular mechanisms and factors that direct cytoplasmic mRNAs between the translational and decay machineries or guide them to RNA granules for storage may have a great impact on the process of ageing and the development of diseases. However, current knowledge of their significance in the modulation of the ageing process and its consequences is limited. In this review, we summarize recent advances in understanding the relationship between mRNA decay and ageing and discuss the impact of key ageing modulators on mRNA turnover and vice versa. In particular, we first address the cytoplasmic mRNA decay processes that determine the half-life of normal and aberrant transcripts focusing on the latest discoveries in the field. Next, we briefly describe the major ageing pathways and mechanisms that affect lifespan in many species. Finally, we present critical findings that link mRNA decay and ageing modulators, supporting a functional interplay between them. Emphasis is given on cytoplasmic RNA granules and their factors that control mRNA turnover under normal and stress conditions, discussing their possible implications in the modulation of ageing.

2. Cytoplasmic mRNA turnover

Degradation of cytoplasmic RNAs is an essential cellular process, serving as a key regulator of gene expression at the post-transcriptional level, under various conditions of growth. Proper regulation of the mRNA decay process is critical for eukaryotic cells to maintain their homeostasis, not only by degrading transcripts that are no longer needed or aberrant transcripts that could lead to the production of toxic proteins, but also by stabilizing or

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destabilizing specific mRNAs, thus allowing a rapid fine-tuning of gene expression under changeable conditions. The fate of mRNAs in the cytoplasm is determined by a common cellular strategy: packaging of mRNAs with proteins into messenger ribonucleoprotein complexes (mRNPs) that regulate mRNA turnover.

2.1. Typical mRNA decay pathways

An ordinary mature mRNA consists of the spliced coding region, 3' and 5' untranslated regions (UTRs) that contain regulatory sequences important for stability and translation, as well as two extra regulatory elements that play a central role in splicing, polyadenylation, nuclear export, translation and degradation of the transcript: a cap structure at their 5' end and a stretch of adenine residues (poly(A)-tail) at their 3' end. The 5'-cap consists of methylated or trimethylated guanine and is added shortly after the initiation of transcription, while the poly(A)-tail is added during transcriptional termination of all transcripts (with the exception of histone mRNA). Both structures protect the mRNA from degradation and promote interactions that facilitate translation initiation in the cytoplasm, through 'circularization' of the mRNA molecules (Preiss and Hentze, 2003). The length of poly(A) tail provides a first level of translational control (Weill et al., 2012), with long tails having a stabilizing effect in the bulk of mRNAs, whereas poly(A)-tail shortening (deadenylation) generally initiates the degradation of mRNAs (Fig. 1).

Deadenylation is mainly executed by the combined action of PAN2/PAN3 and CCR4/NOT deadenylation complexes (Wahle and Winkler, 2013) and, in most cases, is the rate limiting step of cytoplasmic mRNA decay, but is still reversible. Following deadenylation, the mRNA can be degraded in the 3'→5' direction through the action of the cytoplasmic RNA exosome, a multisubunit complex containing the DIS3 exoribonuclease. Most often though, deadenylation is followed by the removal of the 5'-cap by the decapping enzyme DCP2, exposing the 5' end monophosphorylated RNA to exoribonucleolytic degradation by the cytoplasmic 5'→3' exoribonuclease XRN1 (Garneau et al., 2007). DCP1 is an essential cofactor of DCP2 in budding yeast *Saccharomyces cerevisiae*, as it interacts directly with, and introduces conformational changes in DCP2, stimulating its activity. The DCP1/DCP2 decapping complex is conserved in higher eukaryotes but additional factors are needed for their interaction (Jonas and Izaurralde, 2013). Also the DCP1/DCP2 complex communicates with a variety of enhancers or activators that act in diverse ways to stimulate decapping activity (Arribas-Layton et al., 2013). These enhancers may serve as a scaffold for complex assembly or stimulate decapping activity indirectly by repressing translation initiation.

In addition to DCP2, a second mammalian mRNA decapping enzyme, termed NUDT16, with no obvious ortholog in *S. cerevisiae*, *Caenorhabditis elegans* or *Drosophila melanogaster*, has been found to regulate the stability of a subset of mRNAs, at least in some tissues (Song et al., 2010). Further data suggest that both DCP2 and NUDT16 decapping enzymes could be differentially utilized for specific cellular mRNA decay processes (Li et al., 2011). Likewise it was shown that the scavenger decapping enzyme, DCPS in mammals or DCS1 in yeast, can regulate mRNA stability in a transcript-selective manner, acting in conjunction with or as co-factor of the 5'→3' exoribonuclease XRN1 (Zhou et al., 2015). DCPS/DCS1 is known to hydrolyze *in vitro* the residual cap structure from 3' end decay (m^7GpppN), but its role in the degradation of the product generated by 5'→3' decay (m^7GDP) pathway was unclear (Milac et al., 2014). Recent data revealed the existence of a complex process for the elimination of all free cap structures, arising as a consequence of both 5'→3' and 3'→5' mRNA decay pathway and involves DCPS/DCS1 as well as a new scavenger decapping enzyme, named APH1 in yeast or FHIT in mammals (Taverniti and Seraphin, 2015).

The two directions described above, 5'→3' and 3'→5', of cytoplasmic mRNA degradation represent the major decay mechanisms, at least in *S. cerevisiae*, and are both dependent on deadenylation. Recently, an alternative to these mRNA decay pathways has been identified in fission yeast *Schizosaccharomyces pombe* and human cells (Lubas et al., 2013; Malecki et al., 2013; Rissland and Norbury, 2009). It involves the uridylation of adenylated or deadenylated mRNAs, that is the addition of a short stretch of uridyl residues -often only one or two- at their 3' end by terminal uridylyl transferases (TUT4/7) and subsequent decay by multiple ways; decapping and 5'→3' degradation by XRN1 exoribonuclease, 3'→5' degradation by exosome or, degradation by a novel 3'→5' exoribonuclease, named DIS3L2, which functions independently of the exosome. Uridylation was known to be a critical step for the degradation of non-polyadenylated histone mRNAs in mammals, but the above studies suggest that addition of a uridine (U)-tract at the 3' end, of both coding and non-coding RNAs, is a broad phenomenon determining RNAs half-life (Lim et al., 2014).

2.2. Specialized mRNA decay pathways

Eukaryotic cells have also evolved specific pathways for the recognition and degradation of aberrant transcripts in a deadenylation-independent manner. Their major surveillance pathway is the nonsense mediated decay (NMD) that serves in the elimination of mRNA molecules harboring a premature translation stop codon (PTC) (Behm-Ansmant et al., 2006), albeit specific natural mRNAs can be also regulated by NMD in many organisms (Peccarelli and Kebaara, 2014). The recognition of a PTC during translation leads to translational repression, ribosome release/recycling and accelerated mRNA decay by either endonucleolytic cleavage or recruitment of decapping enzymes, the 5'→3' exoribonuclease XRN1 and various exosome components, promoting degradation of the targeted mRNA in both directions (Kervestin and Jacobson, 2012). A second surveillance mechanism, the no-go decay (NGD), is activated when translational elongation is stalled due to a wide range of events, including strong secondary structures or contiguous rare codons. NGD leads to endonucleolytic cleavage and subsequent degradation of the 5' and 3' products (Doma and Parker, 2006). Finally, the non-stop decay pathway (NSD) is triggered when ribosomes fail to encounter an in-frame stop codon during translation, reaching the poly(A)-tail of the transcript. Stalled ribosomes at the 3' end of mRNAs lead to the recruitment of the SKI complex, causing rapid degradation by the exosome, while a contribution of the 5'→3' degradation machinery is possible (van Hoof et al., 2002). An additional specific mRNA decay mechanism is the regulated IRE1-dependent decay (RIDD) that targets mRNAs localized to the ER membrane to maintain ER homeostasis under stress (Hollien et al., 2009) or in certain physiological conditions (Coelho and Domingos, 2014).

Therefore, mRNA decay can be triggered in a transcript-specific manner through the interaction of mRNAs with specific RNA-binding proteins (RBPs). Examples include the UPF proteins that are the key regulators of the NMD pathway or the PUF proteins that recognize specific *cis*-acting elements in 3' UTR of mRNAs and promote translation repression and/or deadenylation, decapping and degradation across species (Miller and Olivas, 2010). In mammalian cells, a common *cis* element that confers instability to an mRNA is the AU-rich element (ARE), identified in the 3' UTR of 5–8% of human mRNAs, encoding for proteins of diverse functions (Bakheet et al., 2006). Several ARE-binding proteins (ABPs) have been identified, including the HuR, AUF1, BRF, TIA-1 and TTP, which regulate mRNA stability and translation through their interaction with AREs. Some of the ABPs stimulate rapid degradation of