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Review

Nuclear retention of mRNAs – quality control, gene regulation and human disease

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ABSTRACT

Nuclear retention of incompletely spliced or mature mRNAs emerges as a novel, previously underappreciated layer of gene regulation, which enables the cell to rapidly respond to stress, viral infection, differentiation cues or changing environmental conditions. Focusing on mammalian cells, we discuss recent insights into the mechanisms and functions of nuclear retention, describe retention-promoting features in protein-coding transcripts and propose mechanisms for their regulated release into the cytoplasm. Moreover, we discuss examples of how aberrant nuclear retention of mRNAs may lead to human diseases.

Contents

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1. Introduction

Eukaryotic gene expression is compartmentalized into nuclear and cytoplasmic mRNA processing events, which are connected through the export of mature mRNAs through the nuclear pore. Nuclear and cytoplasmic processing steps are themselves interconnected and interdependent [1]. For example, during transcription in the nucleus, precursor-mRNAs (pre-mRNAs) are immediately capped at their 5′ ends. As soon as the first splice sites (ss) appear, the spliceosome assembles and pre-mRNAs undergo co-transcriptional splicing to remove non-coding introns and join coding exons. Whereas splicing of first introns feeds back on transcription elongation, the efficiency of last intron splicing affects cleavage and polyadenylation (CPA) of mRNAs [2–4]. In turn, the efficiency of CPA affects the rate of termination, the release of mature mRNAs from the chromatin, their export to the cytoplasm as well as their sensitivity to nuclear decay [5–7]. All mRNA processing steps are catalyzed, coordinated and connected by RNA-binding proteins (RBPs) that tightly bind to mRNAs to form messenger ribonucleoproteins (mRNPs).

To ensure the integrity of gene expression, cells have evolved several fail-safe mechanisms to avoid premature release of pre-mRNAs or improperly spliced mRNAs to the cytoplasm, which would result in the production of nonfunctional and deleterious proteins that cause cell stress, cell death or diseases including cancer [8]. First, core splicing factors are generally confined to the nucleus and do not shuttle to the cytoplasm. Second, many RBPs act as mRNP checkpoints by signalling the successful completion of processing steps in the pathway and thereby discriminate between correctly processed and aberrant RNA products [9]. Third, splicing is precisely coordinated with mRNA export, so that mRNA export factors are only recruited to pre-mRNAs once they have either engaged in or completed splicing [10]. Fourth, export-competent mRNPs are controlled at the nuclear pore and faulty mRNPs are actively retained in the nucleus [11–13]. And finally, in cases where nuclear retention fails and incompletely spliced mRNAs reach the cytoplasm, they are recognized and eliminated *via* the nonsense-mediated mRNA decay (NMD) pathway [14,15].

Nuclear retention of pre-mRNAs is well described in yeast, but recent studies raised the suspicion that in mammalian cells, retention of incompletely spliced mRNAs differs mechanistically [14,16,17]. This is not surprising, as only 5% of yeast genes contain introns (usually only one), and those normally do not undergo alternative splicing. Inhibition of splicing in yeast results in the accumulation of pre-mRNAs at their transcription sites due to inefficient polyadenylation and stalling of RNA polymerase II (pol II), which remains tethered to chromatin. These stalled pre-mRNAs are ultimately degraded by the nuclear exosome [13]. Similar observations were made in mammalian systems using reporter genes with single introns, which reflects the yeast gene architecture. Inhibition of splicing also caused the accumulation of reporter pre-mRNAs at their transcription sites with stalled pol II at their 3′ ends. Inefficient 3′ end processing renders these reporter transcripts sensitive to degradation by the nuclear exosome [6,18]. However, most mammalian transcripts have multiple introns and undergo extensive alternative splicing and use additional splicing signals and splicing factors that do not exist in yeast [19,20].

Most of our knowledge about nuclear retention of endogenous pre-mRNAs in mammalian systems stems from the characterization of different anti-tumor drugs, such as spliceostatin A (SSA), that act as selective splicing inhibitors and block spliceosome assembly and maturation at different steps. Several studies reported that global splicing inhibition, either *via* depletion of spliceosomal components or after SSA treatment, caused the stable accumulation of unspliced polyadenylated mRNAs in the nucleus within enlarged nuclear speckles (NS) [6,14,17,21]. These findings suggested i) that these subnuclear domains might play an important role in the retention and quality control of unspliced mRNAs, ii) that unspliced transcripts are polyadenylated and released from chromatin, and iii) that export-incompetent mRNAs are not immediately targeted by the nuclear exosome. Interestingly, a small fraction of unspliced mRNAs leak to the cytoplasm after SSA treatment. These transcripts are shorter, contain fewer introns and harbor weaker 5′ss compared to retained transcripts, suggesting that these features promote the escape from nuclear retention and degradation by NMD in the cytoplasm [14,22,23].

Mammalian nuclei retain not only unspliced mRNAs, but also mature mRNAs. This phenomenon was noted early on and was reported for only a handful of mRNAs [24–26], but the possible significance for gene expression has been long ignored. However, several recent genome-wide studies using different mouse and human tissues identified a wealth of different mRNAs that are retained in the nucleus at high levels. These included hyper-edited mRNAs [27], incompletely spliced mRNAs [28–32], intronless transcripts [33,34], as well as fully spliced unedited mRNAs [35–37]. Retained mRNAs displayed half-lives longer than 3 h, indicating that these transcripts are not targeted for rapid degradation by the nuclear surveillance machinery, but rather have very slow export kinetics [26,29]. Interestingly, some retained mRNAs are released into the cytoplasm upon a variety of stimuli, such as stress, differentiation, viral infection, DNA damage or neuronal activation [28,29,32,38]. This suggests that in mammalian cells nuclear retention or regulated selective export emerges as a novel mechanism of gene expression control, which might be used to coordinate the expression of related genes, but so far is poorly understood [39].

In this review, we discuss recent insights into the mechanisms and functions of nuclear retention of protein-coding transcripts in mammalian cells. We describe features of retained transcripts and propose mechanisms for their regulated release or degradation as part of a cellular gene expression program. Moreover, we provide

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