Nonsense-mediated mRNA decay

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Abstract

Translation and mRNA decay are coupled processes; the link is most obvious in the case of NMD (nonsense-mediated mRNA decay). NMD is a mechanism that drastically reduces the level of mRNA harbouring PTCs (premature translation termination codons). The defining event in NMD is premature translation termination and the key question is: what distinguishes premature from normal translation termination? Surprisingly, in mammalian cells, PTC recognition is linked to pre-mRNA splicing. Here, we review the current understanding in view of recent developments.

Current NMD (nonsense-mediated mRNA decay) models

NMD has been studied in several organisms and it appears to be an active process requiring specific trans-acting factors. The better known are the UPF (up frameshift) proteins UPF1, UPF2 and UPF3, which were first identified in Saccharomyces cerevisiae and later found to be essential for NMD in all organisms studied. NMD probably serves as a surveillance mechanism that prevents the accumulation of aberrant mRNA, which could encode potentially toxic truncated peptides [1].

The mechanism that links NMD to translation is not clearly understood. The most interesting issue to be addressed is how the ribosome is able to differentiate normal translation termination from premature termination. Studies in human cells indicate that PTCs (premature translation termination codons) can trigger NMD only when located upstream of at least one intron. The link between introns and NMD is mediated by the EJC (exon–exon junction complex), which is a multiprotein complex deposited on the exon–exon junction following pre-mRNA splicing [2]. Several EJC components, including Magoh/Y14, eIF4A3 (eukaryotic initiation factor 4A3) and RNPS1 (RNA-binding protein S1), could interact directly with hUPF3B (human UPF3B) [3,4], which is connected to UPF1 by the bridging protein UPF2. UPF1 associates with the ribosome by interacting with the release factors eRF (eukaryotic release factor) 1 and eRF3. The current model in human cells is that NMD takes place if the PTC is located at least 22 nt upstream of the EJC, which recruits and activates UPF proteins [2,5]. However, this EJC-dependent NMD model has been challenged by the recent discovery that in an Ig-μ mini-gene construct NMD could be observed even in the absence of downstream introns. Instead, NMD efficiency could be enhanced by increasing the length of its 3′-UTR (3′-untranslated region) [6]. Another challenging observation was that the level of β-globin mRNA was stabilized by tethering the PABPC1 (PABP [poly(A) binding protein], cytoplasmic 1) to a downstream PTC-proximal position [7]. Collectively, these reports support the view that mammalian NMD may be similar to the S. cerevisiae mechanism, where the main NMD determinant is the distance between the stop codon and the poly(A) tail [8] (Figure 1).

The genome of S. cerevisiae has very few introns and lacks most of the EJC orthologues. It is conceivable that budding yeast may have lost the EJC mechanism or else the EJC-dependent NMD has evolved only in some lineages. Studies in Drosophila melanogaster indicate that NMD is also triggered by an abnormal 3′-UTR, which suggests that the so-called faux 3′-UTR mechanism maybe a more ancient mechanism [9]. The ‘faux 3′-UTR’ model posits that once the ribosome stalls at a normal stop codon, termination occurs normally, because the downstream 3′-UTR will allow interaction between eRF1/3 and PABP. On the other hand, if termination occurs away from the 3′-end, the interaction between PABP and eRF1/3 will be prevented and NMD is activated. The faux 3′-UTR model states that a termination event occurring upstream of a wrongly configured 3′-UTR is intrinsically abnormal and it triggers recruitment of UPF1 and other NMD factors. However, the mechanism is far from understood; for example, it is known that in fact UPF1 is always associated with ribosomes in budding yeast [10]. Notably, the faux 3′-UTR model is incompatible with the observation that NMD in S. cerevisiae can take place in the absence of a poly(A) tail, as seen in mRNA with the 3′-end generated by hammerhead ribozyme; and NMD is still apparent in PABP-deleted strains [11].

EJC-independent link between introns and NMD

In the mammalian systems, along with examples of EJC-mediated NMD, there are also reports that NMD can occur without any downstream intron. Instead, it has been reported that introns can enhance NMD also when located upstream from the PTC. For example, upstream introns...
Current NMD models

(A) Normal termination. When the ribosome encounters the stop codon, eRF1 and eRF3 associate with cytoplasmic PABP and termination occurs efficiently. (B) A faux 3′-UTR-mediated premature termination. When the ribosome encounters an upstream termination codon, interaction between eRF1/3 and PABP is prevented, termination is not efficient and NMD is triggered. (C) EJC-dependent premature termination. Termination occurs upstream of an EJC,ider EJC mediates the association of NMD factors with the terminating ribosome, and NMD is triggered.

Possible models for link between splicing and NMD

(A) Feedback mechanism. NMD in the cytoplasm generates signals, e.g. RNA fragments, which will signal back to pre-mRNA splicing in the nucleus, possibly causing splicing inhibition and accumulation of unspliced transcript. Abbreviations: 4E, eIF4E (eukaryotic initiation factor 4E); CBP, cap-binding complex. (B) Nuclear scanning. Ribosomes associate with spliced mRNA at the site of transcription. Splicing enhances ribosome scanning, and premature termination in trans impairs proper splicing on nearby nascent pre-mRNA. Pol II, RNA polymerase II; U1, U2 and U5/U6 represent the active spliceosome.

eNMD of the Ig-μ, β-globin and human TPI (triosephosphate isomerase) transcripts [12]. It is possible that this position-independent enhancement is simply a consequence of the higher translation efficiency of spliced mRNA [13]. This intron position-independent enhancement of NMD may be a more general mechanism than appreciated. In Schizosaccharomyces pombe, 40% of the genes have introns and it is an interesting system to further investigate the link between introns and NMD. In this organism, NMD can occur independently of introns; for example, in the ade6 gene, a nonsense mutation at codon 26 triggers strong NMD despite the gene not having any introns. However, preliminary studies in our group indicate that introns can enhance NMD of weak substrates (J. Wen and S. Brogna, unpublished work).

We are still far from knowing what is the real link between splicing and translation termination. It could be that the effect of introns on NMD is simply a consequence of spliced mRNA being more efficiently translated [13]. However, it could be the result of a coupling between translation and pre-mRNA processing, which could be mediated by either a cytonuclear feedback mechanism or translation in the nucleus itself, as suggested by recent reports [14,15] (Figure 2).

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References


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