The role of mRNA translation on nonsense-mediated decay inhibition in disorders due to nonsense mutations

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The regulation of gene expression at the post-transcriptional level allows the cells to rapidly adapt to changes in their environment by altering the patterns of gene expression. The detection and degradation of defective and improperly-processed transcripts is essential to ensure that information following the nucleus into the cytoplasm is of high quality prior to translation, thus cells have evolved surveillance mechanisms to guarantee a tight mRNA quality control, acting at several steps of mRNA biogenesis. The most well characterized surveillance mechanism is the nonsense-mediated mRNA decay (NMD) pathway that recognizes and rapidly degrades mRNAs containing nonsense mutations, which create premature termination codons (PTCs). The physiological importance of NMD is to limit the synthesis of C-terminally truncated proteins, protecting the cell from its deleterious dominant-negative or gain-of-function effects. Approximately one-third of all inherited genetic disorders - and many forms of cancer - are due to PTCs, and in many of these cases NMD influences the severity of the clinical phenotype**.** The strength of the NMD response appears to reflect multiple determinants on a target mRNA. We have previously reported that mRNAs containing PTCs in close proximity to the translation initiation codon (AUG-proximal PTCs) can substantially evade NMD. To test the hypothesis that this AUG-proximity effect could be a consequence of cytoplasmic poly(A)-binding protein 1 (PABPC1) position in close proximity to the PTC due to mRNA circularization, the PABPC1-eRF3 interaction was inhibited by RNA interference. The mRNA levels of the NMD-resistant transcript were quantified by RT-qPCR in these conditions. Moreover, the mRNA levels of an NMD-resistant transcript were also analyzed in condition of inhibition of PABPC1-eIF3G interaction by overexpression of PAIP2 protein, as well in conditions of eIF3h- and eIF3f-depletion. Our data show that in these conditions the NMD-resistance of an AUG-proximal nonsense-mutated mRNA can be converted into NMD-sensitiveness, providing evidence for a role of PABPC1 and associated initiation factor in PTC definition. Such results might benefit the development of therapies that selectively induce ribosomal read-through of PTCs, but not normal termination codons, to treat diseases specifically caused by nonsense mutations.