The interplay between mRNA translation and nonsense-mediated decay in transcripts with short open reading frames

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NMD is one of the better characterized quality control mechanisms which acts as an mRNA surveillance pathway by degrading transcripts harboring premature translation termination codons (PTCs). However, several studies have also implicated NMD in the regulation of steady-state levels of physiological mRNAs, and examples of natural NMD targets are transcripts containing upstream short open reading frames or with long 3' untranslated regions. Indeed, the strength of the NMD response appears to reflect multiple determinants on a target mRNA. We have reported that human mRNAs with a PTC in close proximity to the translation initiation codon (AUG-proximal PTC), and thus, with a short open reading frame, can substantially escape NMD. Our data support a model in which cytoplasmic poly(A)-binding protein 1 (PABPC1) is brought into close proximity with an AUG-proximal PTC via interactions with the translation initiation complexes. This proximity of PABPC1 to the AUG-proximal PTC allows PABPC1 to interact with eRF3 with a consequent enhancement of the release reaction and repression of the NMD response. Here, we provide strong evidence that the eIF3 is involved in delivering eIF4G-associated PABPC1 into the vicinity of the AUG-proximal PTC. In addition, we dissect the biochemical interactions of the eIF3 subunits in bridging PABPC1/eIF4G complex to the 40S ribosomal subunit. Together, our data provide a framework for understanding the mechanistic details of PTC definition and translation initiation.