Nonsense-mediated decay resistance of AUG-proximal nonsense-mutated transcripts relies on the interaction of PABPC1 with the translation initiation complex

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Nonsense-mediated mRNA decay (NMD) is a surveillance pathway that recognizes and rapidly degrades mRNAs containing a premature termination codon (PTC). The unified model for NMD proposes that the decision of NMD triggering is the outcome of the competition between the cytoplasmatic poly(A)-binding protein 1 (PABPC1) and the NMD effector UPF1 for the termination complex. Consequently, PTCs located far, in a linear sense, from the poly(A) tail and associated PABPC1, in mRNAs containing downstream exon junction complexes (EJCs), are expected to elicit NMD. Nevertheless, we have reported that human β-globin mRNAs containing PTCs in close proximity to the translation initiation codon (AUG-proximal PTCs) can substantially evade NMD. We have reported that translation termination at an AUG-proximal PTC lacks the ribosome stalling that is evident in an NMD-sensitive PTC. In fact, we have shown that the establishment of an efficient translation termination reaction at the AUG-proximal PTC is dependent on PABPC1 interaction with the initiation factor eIF4G and with the release factor eRF3 at the terminating ribosome. These interactions underlie critical 3'-5' linkage of translation initiation with efficient termination at the AUG-proximal PTC and contribute to an NMD-resistant PTC definition at an early phase of translation elongation. Furthermore, we provide strong evidence that the eIF3 is involved in delivering eIF4G-associated PABPC1 into the vicinity of the AUG-proximal PTC. This work corroborates a role for PABPC1 on NMD evasion of transcripts carrying an AUG-proximal PTC and provides further insights into the mechanistic details of PTC definition and translation initiation.