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Pentatricopeptide repeat (PPR) RNA binding proteins regulate mRNA processing in mitochondria of Trypanosoma brucei

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Abstract

The majority of mitochondrial pre-mRNAs in trypanosomes undergo massive uridine insertion/deletion editing to create open reading frames. Although required, editing is not sufficient to produce most of translationally-competent mitochondrial mRNAs. Pre and post-editing adenylation and uridylation reactions are essential for mRNA stabilization and ribosome recruitment. Adenylation prior to editing by KPAP1 poly(A) polymerase stabilizes transcripts that are edited beyond few initial sites, while A/Utailing by KPAP1 and RET1 TUTase commits the fully-edited mRNA for translation. Temporal separation of these events suggests that a mechanism must exist to prevent premature A/U-tailing and to couple the completion of editing with A/U-tailing. To identify protein factors responsible for mRNA 3' modification and coordination with editing, we built a comprehensive protein interactions network of mRNA polyadenylation, editing and translation complexes.

RNAi knockdowns, in vivo RNA binding sites mapping and in vitro reconstitution indicate that pre-mRNA is initially stabilized by binding of a specific pentatricopeptide repeat-containing protein (PPR). This factor, termed Kinetoplast Polyadenylation Factor 3 (KPAF3), defines the 3' end of pre-edited mRNA by impeding mRNA degradation by the 3' processome. KPAF3 also stimulates KPAP1's poly(A) polymerase activity to ensure that only A-tailed mRNAs proceed through the editing pathway. We also identified a distinct PPR factor, KPAF4, that binds to a junction between the mRNA and poly(A) tail and blocks premature A/U-tailing. These findings will be presented in a context of integrating editing, polyadenylation and uridylation processes with mRNA selection by the ribosome.

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