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Uridylation-induced RNA degradation in mitochondria of trypanosomes: mechanisms, targets and evolution

Massive U-insertion/deletion mRNA editing in mitochondria of trypanosomes inspired earlier efforts to discover enzymes responsible for RNA uridylation. Studies of RNA editing ultimately led to identification of two terminal uridyltransferases (TUTases): RNA editing TUTase 1 (RET1) and RNA editing TUTase 2 (RET2). Subsequent work demonstrated that RET2 functions as subunit of the RNA editing core complex and is responsible for internal mRNA editing. Conversely, RET1 was implicated in 3' modification of mRNA, rRNA and guide RNAs. Recently, we identified a protein complex composed of RET1 TUTase, DSS1 3'-5' exonuclease and three additional subunits. This complex, termed mitochondrial 3' processome (MPsome), is responsible for primary uridylation of ~800-nt gRNA precursors, their processive degradation to a mature size of 40-60 nucleotides and secondary U-tail addition. Both strands of the gRNA gene are transcribed into sense and antisense precursors of similar lengths. Head-to-head hybridization of these transcripts blocks symmetrical 3'-5' degradation at a fixed distance from the double-stranded region. Together, our findings suggest a model in which gRNA is derived from the 5' extremity of a primary molecule by uridylation-induced, antisense transcription-controlled 3'-5' exonucleolytic degradation. Remarkably, we also established that MPsome-catalyzed 3'-5' degradation also represents the major pathway for mRNA processing and degradation. These finding poses a logistical challenge to the established paradigm of multicistronic mitochondrial transcription and raises the questions of mRNA 5' end modification and 3' end definition. We will discuss potential existence of gene specific promoters and the role of MERS1 NUDIX hydrolase in mRNA 5' processing and stabilization. We will also present data demonstrating that, in contact to antisense RNA-based 3' end definition of gRNAs, the mature 3' ends of pre-mRNAs are generated by protein-based mechanism that blocks the MPsome and stimulates mRNA polyadenylation.

Biography

Ruslan Afasizhev has completed his PhD from Institute of Molecular Biology, Russian Academy of Sciences. He is a Professor of Molecular and Cell Biology at Boston University Medical Campus, USA. He has published more than 50 papers in high ranking journals.

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