

# Role of the isoforms of human eukaryotic release factor 1 in termination of translation

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Eukaryotic release factor 1 (eRF1) is a protein that carries out translation termination in eukaryotes. In humans, eRF1 is encoded by the *ETF1* gene located on chromosome 5. There are six known transcriptional variants (TV) of the *ETF1* gene resulting from alternative splicing. TV1 (NM\_004730.4) encodes the major isoform eRF1 – iso1. More than 95% of all *ETF1* gene transcripts expressed in healthy tissues are TV1. Our analysis of the Ribo-Seq data of human cells and tissues showed that all the other TVs of the *ETF1* gene encode an isoform shortened from the N-terminus by 33 amino acid residues – eRF1 iso2. In addition, Ribo-Seq data shows that transcript TV1 contains an upORF, from which a small peptide (35 amino acid residues) is translated. Interestingly, this peptide is encoded in the same frame as eRF1 iso1, and their sequences are separated by the stop codon UAG and the “linker” GGGGEK. It is known that UAG can be suppressed by some tRNAs. Thus, with a certain probability, eRF1 iso1 can be extended from the N-terminus (eRF1 long). In this study, we obtained recombinant eRF1 iso1 and eRF1 iso2, as well as a peptide with upORF and a hypothetical longer isoform of eRF1 and tested their translational activity in *in vitro* systems. Our data show that eRF1 iso2 recognizes stop codons but is unable to hydrolyze peptidyl-tRNA. eRF1 iso2 binds to eRF3, but the resulting complex is functionally inactive. The activity of longer eRF1 in translation termination is comparable to that of eRF1 iso1. A peptide with upORF in high concentrations suppresses translation termination. We assume that eRF1 isoforms are involved in the regulation of translation termination.

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