ABSTRACT

How far 'AUG-proximity effect' goes?

Francisco J.C. Pereira[1], Alexandre Teixeira[1,4], Jian Kong[2], Ana Luísa Silva[1,3], Stephen A. Liebhaber[2] and Luísa Romão[1,3]*

Nonsense-mediated mRNA decay (NMD) is a surveillance pathway that recognizes and selectively degrades mRNAs carrying premature termination codons (PTCs). We have previously shown that mRNAs carrying a PTC located in close proximity to the translation initiation AUG codon escape NMD. This was called the "AUG-proximity effect". The present work illustrates that the extension of the AUG-proximity effect, i.e. to what position in the open reading frame (ORF) an AUG-proximal PTC does not trigger NMD, is different between human α- and β-globin mRNAs. Remarkably, our data also demonstrate that, contrary to what occurs in the β-globin transcripts, α-globin mRNAs carrying an AUG-proximal PTC allow for efficient translation re-initiation, although it only partially explains their NMD resistance. In addition, our results reveal that in the α- and β-globin transcripts, the extension of the AUG-proximity effect is determined by the ORF sequence. Furthermore, we show how the mRNA secondary structure, which is affected by the ORF sequence, determines the AUG-proximity effect extension. Our data point out that the time taken to translate the short ORF, affected by its sequence and stability, besides being involved in modulating translation re-initiation, also plays an important role in establishing the extension of the AUG-proximity effect.

[1]Departamento de Genética, Instituto Nacional de Saúde Dr. Ricardo Jorge, 1649-016 Lisboa, Portugal
[2]Departments of Genetics and Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA
[3]Universidade de Lisboa, Faculdade de Ciências, BioFIG - Center for Biodiversity, Functional and Integrative Genomics, Lisboa, Portugal
[4]Universidade Nova de Lisboa, Faculdade de Ciências Médicas, CIGMH - Centro de Investigação em Genética Molecular Humana, Lisboa, Portugal
*Corresponding autor