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NAIST researchers are exploring the quality control function of the Upf1 enzyme in the protein production process.

Cell biology

Key quality control element revealed

An RNA-scanning mechanism may help cells prevent production of potentially toxic truncated proteins

A mutation affecting a single nucleotide can be sufficient to interrupt the synthesis of a protein, resulting in a truncated product that may potentially disrupt the normal function of the cell. Researchers led by Yasumasa Ishida of NAIST have uncovered a ‘quality control’ mechanism that help detect and eliminate these prematurely-shortened RNA molecules¹.

Within every messenger RNA (mRNA) resides the recipe for building a protein, composed of a series of three-nucleotide ‘codons’ that each encode a particular amino acid. These instructions are concluded by one of three different ‘stop codons’, which terminate protein production. Genetic alterations can convert an amino acid-encoding codon into a stop codon, interrupting the translation of the affected mRNA prematurely. These molecules are selectively recognized and eliminated via a mechanism known as ‘nonsense-mediated decay’.

Ishida’s team wanted to explore how Upf1, a ‘molecular motor’ enzyme with the

capacity to travel along RNA and DNA strands, contributes to this process. Before an mRNA can be translated into protein, it undergoes a splicing process that removes various non-protein-coding segments; these splice sites are marked by assemblies of proteins known as the exon-junction complex (EJC), which get removed as the mRNA undergoes translation. In principle, a prematurely terminated mRNA with a nonsense mutation will retain at least some of these EJCs intact. Ishida and colleagues experimented with various synthetic mRNAs to examine how interactions between Upf1 and EJC contribute to nonsense-mediated decay.

Upf1 is associated with the protein translation machinery, and Ishida’s team found evidence that this protein uses its motor activity to essentially ‘reel in’ the mRNA strand after protein translation becomes stalled. If this halt is due to a true stop codon, the translation machinery disassembles, and the mRNA is released intact. In the event of a nonsense

mutation, Upf1 scans until it encounters an EJC; this interaction sets the nonsense-mediated decay process in motion, eliminating the damaged mRNA strand.

These data suggest that Upf1 fulfils a critical quality control function to restrict the production of defective — and possibly toxic or tumorigenic — proteins. If future studies validate this model, it could also fill in critical gaps in our understanding of the protein production process. “People still do not know how a normal cycle of protein translation really ends,” explains Ishida. “Our ‘reeling-in’ model could beautifully explain both ribosome recycling, which is the last step of a normal cycle of protein translation, and nonsense-mediated decay in a unified manner.”

Reference

1. Shigeoka, T., Kato, S., Kawaichi, M. & Ishida, Y. Evidence that the Upf1-related molecular motor scans the 3'-UTR to ensure mRNA integrity. *Nucleic Acids Research* **40**, 6887–6897 (2012).