Why mRNAs blueprints that are more difficult to decipher have shorter lifetimes

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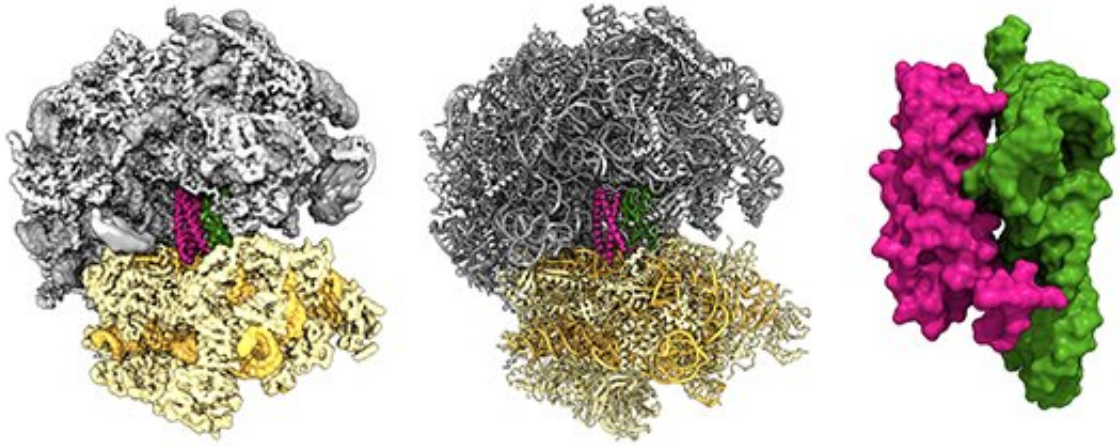

Structure of the Not5-ribosome complex. Cryo-EM density of the Not5-80S ribosome complex (left). Molecular model of the Not5-80S ribosome complex (middle). Surface representation of the Not5-tRNA interaction (right). The 40S ribosomal subunit is colored in beige, the 60S subunit is colored in grey, the tRNA is colored in green and Not5 is colored in pink. Credit: R. Buschauer

mRNAs program the synthesis of proteins in cells, and their functional lifetimes are dynamically regulated. LMU researchers have now shown why blueprints that are more difficult to decipher have shorter lifetimes than others.

The control of gene expression is a fundamental component of living systems. The term refers to the suite of mechanisms that determines how

the hereditary information encoded in the DNA genome of every cell is selectively transcribed into messenger RNAs (mRNAs), and then translated by ribosomes into proteins. Because the set of proteins synthesized in a cell defines its structure and biochemical capacities, every step in the process must be tightly regulated. One of the modules of this regulatory system is dedicated to the timely destruction of mRNAs in response to changing conditions. An international team led by Professor Roland Beckmann at LMU's Gene Center, in collaboration with Jeff Coller (Case Western Reserve University, Cleveland, U.S.) and Toshifumi Inada (Tohoku University, Sendai, Japan) has now worked out the detailed structure of a protein complex that is involved in mRNA degradation, and dissected its mode of action. The results of the new study, which appears in the journal *Science*, explain how and why the lifetime of an mRNA molecule is linked to the rate of synthesis of the protein it encodes.

"Statistical data had already revealed that the lifetime of an mRNA is correlated with speed of the ribosome during synthesis of its protein product," says Robert Buschauer, a Ph.D. student in Beckmann's group and lead author of the new paper. "But the molecular basis for this relationship was completely unknown."

The efficiency of protein synthesis largely depends on how well the ribosome can read the instructions encoded in the nucleotide sequences of mRNAs. These programs are written in the language of the genetic code. Triplet sequences of nucleotides ('codons') specify the order in which the different amino acids that make up the protein are linked together. Each of the required set of amino acids is delivered to the ribosome by an adaptor molecule called a tRNA. Each tRNA is also equipped with a nucleotide triplet (an 'anticodon') that recognizes its counterpart in the mRNA, and this interaction enables its amino-acid cargo to be slotted into the correct position in the growing protein. The genetic code is redundant: virtually all amino acids are specified by

several nucleotide triplets, which are read with varying efficiencies by the ribosome. If a given triplet is difficult to read, the ribosome takes longer to select the appropriate tRNA with the required amino acid. The new study identifies the mechanistic basis for the link between this delay and the degradation of mRNAs. "With the aid of cryo-electron microscopy, we were able to show that a key protein complex that is required for mRNA degradation can interact with the ribosome only if the tRNA binding site is not occupied." This finding explains why the probability that an mRNA molecule will be degraded on the ribosome rises with the fraction of inefficiently decoded codons it contains.

"This newly discovered interaction is in fact crucial for the coupling between mRNA degradation and ribosomal efficiency," says Beckmann. The destruction of mRNAs is an essential process, whose central components differ very little between yeast and human cells. Any errors that occur can give rise to neurodegenerative diseases, cancers or other serious disorders. A better understanding of the underlying mechanisms is therefore a prerequisite for the development of more effective therapies.

More information: Robert Buschauer et al. The Ccr4-Not complex monitors the translating ribosome for codon optimality, *Science* (2020). DOI: 10.1126/science.aay6912

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