'Rhythm' of protein folding encoded in RNA, biologists find

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Researchers Sebastian Pechmann and Judith Frydman

(Phys.org)—Multiple RNA sequences can code for the same amino acid, but differences in their respective "optimality" slow or accelerate protein translation. Stanford biologists find optimal and non-optimal codons are consistently associated with specific protein structures, suggesting that they influence the mysterious process of protein folding.

Your average musical melody doesn't chug along at a single, mechanical speed. It mixes whole notes, quarter notes, sixteenth notes and so on to lay out a specific, complex rhythm.

It looks like protein synthesis may work the same way.

The sequence of events is elegant: proteins are assembled when ribosomes match mRNA sequences up with specific tRNA molecules. Those tRNAs carry specific amino acids that link together in a chain to form a specific protein.

But multiple RNA sequences can encode the same amino acid – some that are translated quickly, and some slowly. Although they all result in proteins with identical composition, the choice of mRNA sequence can dramatically change the rate at which the protein is made.

Research from Stanford biology Professor Judith Frydman and researcher Sebastian Pechmann now reveals that this protein synthesis "rhythm" may be evolutionarily adjusted to control the folding of the new protein chain as it emerges from the ribosome.

The finding may explain how RNA sequences define the final, folded form of a protein – a fundamental problem in molecular biology, since proteins need to fold in order to function.

"For around 50 years, there has been a conceptual gap between the sequence and the final structure," said Pechmann, a postdoctoral scholar in the Frydman Lab. "There's been the sense that there's much more information in the sequence than can be deciphered at the moment."

Published online in advance of print last month in the journal Nature Structural and Molecular Biology, the paper analyzes 10 closely related yeast species as a model. Both fast ("optimal") and slow ("non-optimal")

codons are evolutionarily conserved, consistently appearing in particular parts of the mRNA transcript, where they appear to strategically slow down or speed up translation.

"What they are doing is setting a tune for protein folding," said Frydman.

Not quite synonymous

The tRNA molecules are cloverleaf-shaped twists of RNA that float freely in the cell until called into action by a ribosome. The stem of the clover is linked to an amino acid, while the leaf's middle lobe recognizes the three-nucleotide mRNA sequence, or codon, that corresponds to that amino acid.

This genetic code is partially redundant. Some amino acids are encoded by as many as six different codons. But these sequences, while specifying the same amino acid, aren't all equally available.

Almost all amino acids can be specified by either a fast, available tRNA molecule or a slow, rare one, giving the cell the option of using RNA sequence to regulate translation speed.

"An idea has been around for years that this could define the rhythm of the translation process," said Frydman. "The step of adding an amino acid is very, very important, and if the ribosome makes mistakes or if the protein doesn't fold correctly, the effort expended in making the protein becomes useless."

Rhythm control

Taking into account both the supply of and demand for each tRNA,

Frydman and Pechmann ranked the codons according to their availability and examined where they appeared in the mRNA transcripts of 10 related yeast species. This approach allowed them to look for evolutionarily conserved patterns – as Frydman put it, "using evolution to sort out the noise from the biological signal."

The researchers found that non-optimal codons tended to appear in regions where slower protein synthesis could directly facilitate folding even while the protein was still incomplete.

Clusters of non-optimal codons correspond to specific kinds of protein structures known to fold during translation, such as "a-helices" – right-handed spirals – and loops.

In contrast, optimal codons are translated faster, but also more accurately. They tend to code for protein regions where translational errors would put the protein at an especially severe risk of aggregation – a situation in which large numbers of misfolded proteins clump together.

Such aggregates have been implicated in diseases like Alzheimer's and Huntington's. The researchers speculate that the judicious placement of optimal codons in these aggregation-prone stretches would ensure a high degree of accuracy and a lowered chance of potentially disastrous misfolding.

These findings barely scratch the surface of how codon choice may affect folding. The researchers point out that the cell might even be able to fold, or unfold, a protein into different states simply by modulating tRNA availability. This would adjust the relative optimality of the tRNAs' corresponding codons, potentially altering the rhythm of synthesis.

Designers of new proteins may take note as well. Bioengineers often find

that their creations misfold, even when their amino acid sequences match natural structures exactly.

"The commonly used strategy to select optimal codons when making synthetic genes often fails," Pechmann said. "A rational understanding of codon sequence optimization will be fundamental for biotechnological applications… We here clearly demonstrate why you need the non-optimal codons to keep this rhythm intact."

Both researchers are affiliated with the Stanford Bio-X program.

More information: www.nature.com/nsmb/journal/va … t/abs/nsmb.2466.html

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