How ribosomes in our cells enable protein folding

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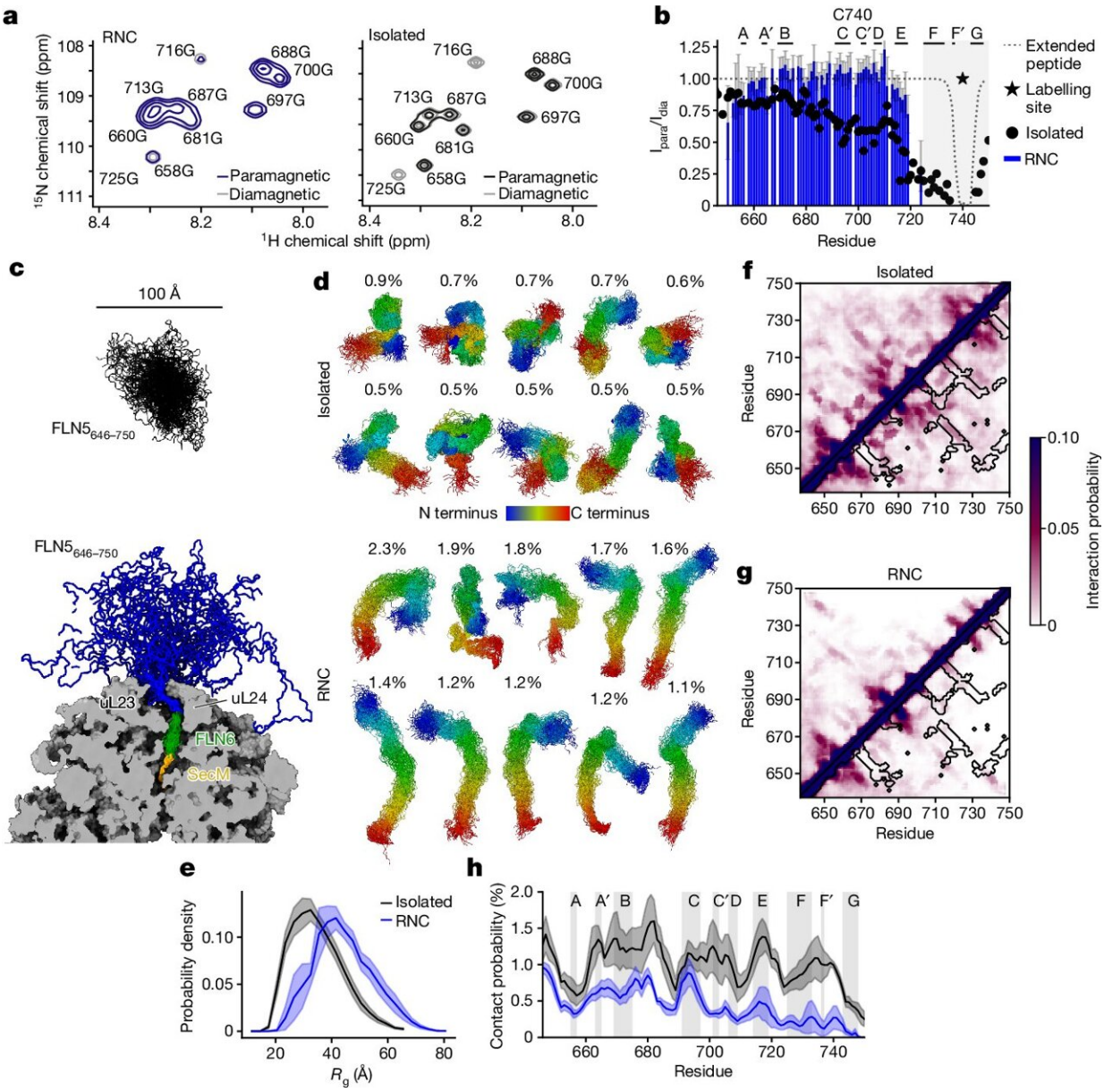

The ribosome modulates the conformational ensemble of the unfolded state. Credit: *Nature* (2024). DOI: 10.1038/s41586-024-07784-4

Scientists at UCL have discovered a novel role played by ribosomes during the folding of new proteins in cells, described in their paper in *Nature*.

Ribosomes, the cell's dedicated molecular machines for protein synthesis , make all proteins in life and do so by piecing together one amino acid building block at a time. As they are being synthesized, these nascent proteins simultaneously attempt to fold while still associated with their parent ribosome, referred to as co-translational protein folding.

Understanding how exactly protein folding occurs remains a key challenge for scientists, and this co-translational folding provides the way in which cells ensure the safe and efficient production and assembly of new proteins in their functional native states. Failure to fold or aberrant folding is associated with a plethora of devastating diseases.

As most of the understanding of protein folding has arisen from lab experiments with isolated polypeptides in bulk solution (not specifically on the ribosome), it has proven difficult to reconcile findings on the ribosome (which is a more typically realistic experimental setting) that show considerable differences in folding to those seen from isolated refolding studies.

In the new paper, scientists have revealed that ribosomes are even more important to the folding process than previously believed, as they direct folding pathways by impacting the energy and stability of the new peptide chains.

By experimentally capturing and imaging snapshots of protein synthesis of nascent chains on their ribosomes, the researchers have discovered the structural basis of how the thermodynamics of co-translational protein folding is distinct to that in bulk solution by showing that ribosomes affect the global properties of unfolded proteins.

They found that on the ribosome, unfolded proteins adopt expanded structures, while off the ribosome they become more compact and spherical. This so-called "entropic destabilization" of the unfolded state is the main driver of how the ribosome alters the protein folding pathway via aiding the formation of co-translational folding intermediates. These are discrete partially folded forms of the nascent protein that are absent or highly unstable in isolation, yet long-lived on the ribosome.

These thermodynamic effects also contribute to the ribosome protecting the nascent proteins from mutation-induced unfolding. This implicates co-translational folding as a crucial mechanism that facilitates protein evolution productively, through facilitating protein assembly during biosynthesis, but also perhaps facilitating potentially harmful misfolding events linked to disease—demonstrating how the ribosome is both essential to life in its facilitation of protein folding but can also be involved in disease.

Lead author Professor John Christodoulou (UCL Structural & Molecular Biology) said, "We have found that ribosomes are even more important to protein folding and misfolding processes than previously believed, suggesting that future research into this vital component of life should incorporate the role of ribosomes.

"The majority of proteins can only fold to their active forms during their biosynthesis on the ribosome so an understanding of the process and in particular of the novel structures of the co-translational intermediates formed can be important for developing understanding disease.

"As some proteins are involved in diseases such as cancers, we are hoping to continue our research to see if these new insights into protein folding on the ribosome could inform new treatment pathways."

More information: Julian O. Streit et al, The ribosome lowers the entropic penalty of protein folding, *Nature* (2024). DOI: 10.1038/s41586-024-07784-4

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