Cotranslational folding and evolution of repeat proteins.

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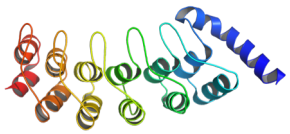

It is increasingly clear that ribosomes modulate protein folding during translation. For instance, computational studies have detected evolutionary selection for slowly translated codons that correlate with cotranslationally folded intermediates of subdomain size. Additionally, it was experimentally demonstrated that the rate at which the nascent chain emerges could determine alternative folded structures. Besides, state of the art tools for homology detection have allowed the discovery of evolutionarily conserved subdomain-sized fragments (of ≈ 40 aa) in seemingly unrelated proteins. These fragments frequently constitute the smaller sub-units of repetitive domains such as Pentarepeat β-helix repeat, Ankyrin repeat or Leucine-rich repeat. Our work has demonstrated that polypeptide chains up to ≈ 70 residues can fold in the ribosomal exit tunnel; it is therefore tempting to speculate that the tunnel facilitates the folding of the small units (≈ 20-35 aa) that compose large repetitive proteins. In fact, by using arrest peptides as force sensors we have recently characterized the cotranslational folding of a Pentarepeat β-helix repeat protein that displayed several force peaks; the force of these peaks increase linearly with the length of the translated polypeptide. Additionally the peaks correlate well with the boundaries of repetitive units being the biggest one homologous to a four-coil b-helix protein. Our findings are in line with previous work on the *Drosophila* notch receptor (Ankyrin repeat protein) where an experimental determination of a folding energy landscape shows that the stability of the full domain varies linearly with the number of repeats. In the present work we characterize the cotranslational folding of a range of large repetitive proteins by using arrest peptides as force sensors, bioinformatic tools, and limited proteolysis.

References:

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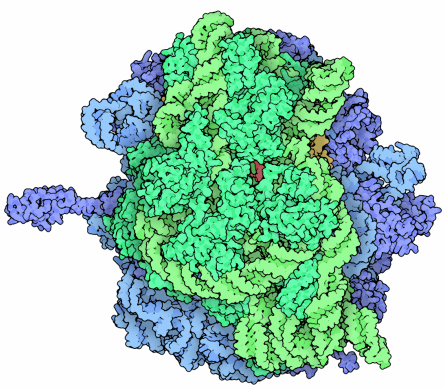

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