Why and how co-translational protein folding supports proper proteome function

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Most complex, multimeric proteins cannot be refolded to high yield from a chemically denatured state. Instead, they misfold and aggregate. Yet many of these proteins fold to high yield in the cell. In vivo, protein folding starts during polypeptide chain synthesis by the ribosome. Vectorial folding of the polypeptide chain from N- to C-terminus during synthesis represents a fundamentally different starting point for folding than diluting a full-length protein from a chemical denaturant. Our laboratory and others have shown that the folding intermediates populated during co-translational protein folding can be distinct from in vitro refolding intermediates. Vectorial folding, along with molecular chaperones and other aspects of the cellular folding environment, can enhance folding yield and suppress misfolding and aggregation, supporting proper proteome function.