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Folding to function

The practice of origami dates from the 1600s, but this cannot compare to how long proteins have been evolving form and function. How proteins achieve their correct shape is the subject of this special Focus.

For those who practice the traditional Japanese art of paper folding, or origami, a sheet of paper can be used to create countless shapes—objects, animals or geometrical forms—via a precise sequence of folds and creases. The level of complexity that can be achieved is impressive, but there are actually only a few folds used in origami, which can be combined in different ways to generate a myriad of shapes. This process is analogous to how polypeptide sequences fold to yield proteins with different structures, properties and functions, a subject that we explore in this issue of *Nature Structural & Molecular Biology*, in a special Focus on Protein Folding.

But the origami analogy is not perfect: instead of a two-dimensional sheet of paper devoid of any instructions, a protein starts as a linear sequence of amino acids, whose particular order ultimately determines its native conformation, usually the most stable, lowest-energy structure. Nonetheless, the art of paper folding is a useful way to illustrate some concepts about protein folding in the cell. When all goes well, you end up with a beautiful and functional structure. When things go wrong (misfolding), you may get a crumpled mess that needs to be smoothed out (unfolding) to try to start the process over again (refolding), or you may just give up and feed it to the shredder for recycling (degradation). Some unfolded or misfolded conformations can aggregate and generate forms that are difficult to degrade, akin to a pile of sheets glued together, and cause cellular toxicity or death. In fact, defects in protein folding have been linked to a number of pathologies where such aggregates (amyloids) are observed, including neurodegenerative conditions such as Parkinson's, Alzheimer's and Huntington's diseases, although what the toxic species are remains to be determined.

Many of these concepts are covered in the Reviews in this Focus, with an emphasis on recent developments in the field. Hartl and Hayer-Hartl (page 574) introduce the basic concepts of protein folding and why molecular chaperones—proteins that assist in the folding process—are needed in the cell and how they operate. Bartlett and Radford (page 582) review the different methodologies that have been used to study protein folding, *in vitro* and *in vivo*, and how their combined use has allowed us to glimpse how complex and baroque protein folding pathways can be. Bukau and colleagues take an in-depth look at the early events in the life of a protein (page 589), as the nascent polypeptide chain emerges from the ribosome and interacts with a multitude of cytosolic factors that

determine its fate within the cell, and how these processes (translation, processing, folding and targeting) can be coordinated.

Two Perspective pieces explore important and still controversial subjects. Prions are proteins that can adopt infectious conformations, and they are implicated in diseases such as bovine spongiform encephalopathy (also known as 'mad cow disease'). The yeast prion [*PSI*⁺] is arguably the best-characterized prion system, combining the power of yeast genetics with more recent biochemical and structural efforts, which are discussed by Tessier and Lindquist on page 598. Finally, integral membrane proteins represent a particular challenge to eukaryotic cells, as their folding occurs concomitantly with the protein's translation and membrane insertion. This process takes place in the context of a translating ribosome bound to the translocon complex in the endoplasmic reticulum membrane, and how it might happen is examined by Skach on page 606.

In addition to these pieces, we would also like to invite you to visit the online features of the Focus. With help from experts in the field, we put together an annotated collection of 'Classics' (<http://www.nature.com/nsmb/focus/protein/classics/index.html>)—landmark papers that shaped and guided research. This compilation provides a historical perspective on how the field has progressed. We have also asked researchers about their views on where the field is going—the 'big questions' that still await answers and the technical developments that will make answering those questions possible; you can read these in 'Looking ahead' (<http://www.nature.com/nsmb/focus/protein/lookingahead.html>). Finally, you can browse a library of recent papers on protein folding published in the Nature Research and Review journals (<http://www.nature.com/nsmb/focus/protein/library/index.html>).

We would like to acknowledge all the scientists who helped us create this Focus issue—of course, the authors who put time and effort into writing (and rewriting) the Reviews and Perspectives, and the reviewers who provided valuable criticism and suggestions to improve the pieces. Many researchers offered their opinion about the timeliness and content of the Focus at its initial stages, and later contributed to the online sections, and we thank them for their input and ideas.

We hope you will enjoy reading the pieces in this Focus and renew your appreciation for how awe-inspiring the process of protein folding really is and how readily it can go awry. ■