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Title: Deciphering disease causality within a potential plethora of protein aggregates

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The relationship between the sequence of a protein as its three-dimensional structure has been known for more than 50 years from Chris Anfinsen's pioneering work. Today our knowledge of protein sequence-structure relationships has culminated in views of proteins folding on robust energy landscapes that are shaped to funnel a polypeptide chain to its native structure, irrespective of changes in sequence and/or solution conditions. But protein folding is not perfect: energy landscapes are rugged and mistakes in folding are made, which are rectified by chaperones or erased by degradation. However, when these systems are overwhelmed, proteins aggregate, forming amyloid fibrils that result in cellular catastrophe. And it is here that a fascinating conundrum faces us: how does protein sequence relate to amyloid fibril structure? How can there be more diseases than there are precursor sequences? And, amongst the plethora of aggregates, which are the culprit(s) of disease?

Recent insights from cryoEM have shown that the same protein sequence can form many different cross-β amyloid folds, a concept badged as structural polymorphism. Indeed, just small changes in pH or buffer salts, the addition of a ligand, a post-translational modification, or a point mutation can easily switch assembly to a new amyloid fold. Recent experiments *in vitro* have also shown that fibril structures change with time, with fibrils formed early differing structurally from those found later in assembly. Hence structure-guided drug design or the development of diagnostics focusing on the end products of disease could potentially miss key agents of disease.

Answering these questions will require detailed structural analysis of the time courses of fibril assembly *in vitro*, in cells, in model organisms and in human disease. Determining which fibril structures can be disassembled by chaperones, which evade detection, and which are recalcitrant to the proteostasis machineries, and how these properties link to cellular dysfunction and disease are the next frontier.