The Catalytic Amyloid Fold as a Solution to the Dilution Problem

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Enzymes posses a complex 3-dimensional fold as a prerequisite for creating a catalytic active site in which a reaction can proceed shielded from the aqueous environment. An apparent prerequisite for biopolymers to fold into stable structures of the kind necessary for aqueous catalysis is that they are large - typical enzymes comprise hundreds of amino acid residues while the smallest known enzymatic units approach 60 residues [1] (and these are only functional as a pentamer). Such a size requirement presents a conundrum for the origin of enzymes in biology. In the absence of a control mechanism (*e.g.* a biological system) any process that synthesizes potential catalytic polymers is by its nature at least partially random. The randomness leads to the dilution problem, meaning that the number of possible polymers quickly grows astronomically large (example: with only 4 different monomers there are 1.6E60 possible sequences of polymers that are 100 residues long). Even if such a large enzyme comes into existence by chance, the underlying problem remains that this molecule has to find a way to generate more of its own before it can become significant to the origins of life.

We have proposed that the amyloid fold, a peptide aggregate with a repetitive pattern of β-strands that lie perpendicular to its long axis, provides a structural scaffold that can overcome this problem [2]. Peptides as short as 4-mers can form this kind of supramolecular assembly meaning that very small peptides can form large complexes with a 'well-defined' 3-dimensional structure [3]. In an effort to probe the catalytic potential of short peptide amyloids we constructed a library of amyloidogenic peptides and set up a simple screening method that is applicable to a high-throughput screen of catalytic activity for thousands of amyloids. Several catalytic entities have been identified in a small library of 33 peptides and larger libraries are currently under investigation.

References: [1] Tiessen A et al. (2012) *BMC Res Notes, 5*, 85. [2] Greenwald J. and Riek R. (2012) *JMB, 421,* 417–426. [3] M. R. Sawaya et al. (2007) *Nature, 447*, 453-457.