Structural and biochemical basis of protein amyloid evolution

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Structural and biochemical basis of protein amyloid evolution

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Research Abstract
Protein misfolding and aggregation into amyloid fibrils is a hallmark of serious diseases such as Alzheimer´s, Familial Amyloidotic Polyneuropathy (FAP) and atherosclerosis. Amyloid fibrils can also be biologically functional. Bacterial and fungal amyloids are proposed to form a prominent

protein fold early in evolution. It is unclear why many different proteins, which often assume stable functional quaternary structure under normal conditions, can convert into a common ?-sheet rich amyloid aggregate. An important unanswered question is whether the molecular mechanisms of amyloid formation have been conserved in evolution. We will characterize these mechanisms using two very different proteins involved in amyloid diseases: apolipoprotein A-I (apoA-I), a helical protein that is important in atherosclerosis and familial amyloidosis, and transthyretin (TTR), a beta-sheet protein that forms amyloid in FAP. We will explore in detail the novel molecular mechanism of amyloid formation by human apoA-I , which will help design a strategy to block this process. We will further characterize amyloid formation in evolutionary diverse species using fish TTR as a model protein that, we previously showed, forms amyloid. Fish are the most biodiverse group of vertebrates that can adapt to broad range of external conditions; hence, they are particularly suitable to study the adaptation of protein structure/function. TTR amyloid formation will be characterized in two evolutionary distinct piscine species with different adaptation mechanisms: a modern Actinopterygii (sea bream) and an ancient Agnatha (lamprey). The role of sea bream TTR N-terminus, previously proposed to be important in amyloid formation, will be investigated and compared with human TTR. The results will provide sharper insights into amyloid formation by structurally and evolutionaly diverse proteins, and will help develop new strategies to block amyloid diseases such as apoA-I amyloidosis, atherosclerosis and FAP.

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