Hiding in Plain Sight—Could a Common Molecular Mechanism Define Neurodegenerative Diseases?

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EDITORIAL

Many neurodegenerative pathologies such as Alzheimer’s (AD), Parkinson’s (PD), Huntington’s (HD), Creutzfeldt Jakob diseases (CJD) etc. are characterized by severe changes in synaptic functions and eventual neuronal death in the brain. Besides this pathological commonality, all these diseases possess a biochemical commonality in which the respective proteins aggregate to form amyloids that are known to be responsible for neuronal cell death. Amyloid formation involves the conversion of proteins from their native monomeric states (intrinsically disordered or globular) to well-organized, fibrillar aggregates in a nucleation-dependent manner. Although amyloid-diseases differ in their functional and some pathological aspects, all amyloidogenic proteins, irrespective of their native structure form a cross β-sheet structural core upon aggregation. Interestingly, the unique ability of this conformation to accommodate tightly packed interactions is reflected in its remarkable conservation among all amyloids, despite significant sequence diversity.

Accumulating evidence indicates pathological links between several amyloid diseases including AD, PD, HD, Prion diseases, systemic amyloidosis etc. Importantly, the links mainly seem to arise due to the interactions between the respective amyloid proteins involved [1-5]. Although pathological basis for such inter-disease interactions is increasingly becoming clear, molecular reasons for these observations are less evident. However, over the last few years a template-assisted corruptive propagation mechanism, which is the hallmark of mammalian prions, is beginning to emerge as a plausible consensus mechanism among many neurodegenerative diseases. More importantly, such a mechanism seems to define the molecular basis of cross-talk between amyloid pathologies. The amyloid aggregates of prion proteins responsible for spongiform encephalopathies such as CJD and Scrapie are one of the first protein conformational diseases known [6]. The mechanisms of infectivity and propagation of prion proteins are now well understood to progress in a protein-only, template-assisted manner resulting in transmissibility and infectivity. Contrary to the earlier thought that primary sequence differences introduce species-specific barriers among prions, emerging evidence support a template-based mechanism in which the effect of sequence in specificity is minimum [10,11]. Although several factors (genetic and environmental) may influence the propagation of amyloid to interact with, and convert the non-toxic form of prion proteins to similar conformationally-altered infectious species, iteratively. Several lines of evidence have emerged recently that suggest a common, prion-type mechanism of disease progression could occur among various neurodegenerative diseases including AD and PD, confirming the long-term speculation based on their pathogenic similarities [7-9]. These reports demonstrate that amyloids of proteins other than prions too, could be transmissible in vivo, and may act like disease-causing prions in eliciting toxicity and perhaps even infectivity. Contrary to the earlier thought that primary sequence differences introduce species-specific barriers among prions, emerging evidence support a template-based mechanism in which the effect of sequence in specificity is minimum [10,11]. Although several factors (genetic and environmental) may influence the propagation of amyloid...
structures from one species to another [12,13], evidence has emerged in support of a protein-only basis for an inter-species transmission [12,14,15]. Many such reports indicate that the conformation of an amyloid seed and not its protein sequence, plays an important role in the corruptive conversion of conformation and propagation.

Based on the increasing body of evidence, it is clear that the following aspects are conserved among various amyloid pathologies: a) convergence to a unique cross β-sheet structure upon aggregation, b) adoption of template-assisted prion-type interactions by respective amyloidogenic proteins, and c) the presence of cross-talks between amyloid pathologies leading to inter-pathology infections. If one could deconstruct and disseminate this information, a new template-based consensus mechanism emerges that forms a common backbone that links many amyloid pathologies. More importantly, it also reveals a promiscuous nature of interactions among amyloids. Such a mechanism would explain the symptoms of multiple amyloid pathologies often observed among neurodegenerative disease patients. This also suggests a more sinister consequence of all amyloids being potentially infectious like prions. Although this remains a hypothesis today, a rigorous research is imperative to precisely decipher this remarkable mechanism, and to be able to make therapeutic advances towards curing some of the most complex diseases in human history.

REFERENCES