Trends in Cell Biology

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Review

Cell Biology of Prions and Prionoids: A Status Report

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The coalescence of proteins into highly ordered aggregates is a hallmark of protein misfolding disorders (PMDs), which, when affecting the central nervous system, lead to progressive neurodegeneration. Although the chemical identity and the topology of each culprit protein are unique, the principles governing aggregation and propagation are strikingly stereotypical. It is now clear that such protein aggregates can spread from cell to cell and eventually affect entire organ systems – similarly to prion diseases. However, because most aggregates are not found to transmit between individuals, they are not infectious *sensu strictiori*. Therefore, they are not identical to prions and we prefer to define them as 'prionoids'. Here we review recent advances in understanding the toxicity of protein aggregation affecting the brain.

Trends

Protein misfolding and aggregation is the root cause of many neurodegenerative disorders. Data implicate oligomeric species in the initiation and propagation of toxicity and in their own self-propagation.

Although chemically disparate, toxic oligomers in various disorders activate similar downstream pathways, suggesting that a limited number of common mechanisms may lead to cytotoxicity.

Pathological protein aggregates use many different cellular mechanisms to spread within organisms. Exosomes may be exploited as Trojan horses by these entities. Several nonconventional pathways may also play a role in the export of oligomeric units, including tunneling nanotubes.

Pathological oligomers can use classical endocytic routes for entry into the cell. However, some oligomers may interact with the plasma membrane and gain entry through nonconventional routes.

PMDs

Alterations in the secondary structure of proteins can lead to the formation of abnormally folded conformers. On reaching critical thresholds, or under the influence of poorly understood triggers, these can seed the formation of ordered aggregates and ultimately lead to PMDs [1,2]. These disorders can occur in many different organs; for example, in the form of amyloidoses in the liver, the spleen, or the peripheral nervous system. This review focuses on PMDs affecting the central nervous system, which include Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and prion diseases. The primary structures of misfolded proteins, and the clinical consequences of their misfolding, vary between these diseases, yet all of these entities share common features including the loss of neurons, abnormalities of synaptic function, and, most conspicuously, the deposition of extracellular or intracellular protein aggregates.

Most evidence indicates a model of disease progression common to all PMDs. Abnormally folded, or partially unfolded, conformers of a disease-associated protein interact with each other to form cross-beta spines [3] that assemble into a 'nucleus', an ordered aggregate possessing the ability to self-propagate. Therefore, such nuclei were appropriately called 'propagons' [4] even if the propagation process is incompletely understood. Propagons may accrue additional monomeric protein from their environment, possibly by exploiting transient semi-unfolded states. Since accretion typically occurs along a single axis, its product is not a 3D crystal but rather filamentous structures sometimes called protofilaments. Multiple protofilaments can interact with each other and form higher-order fibrillary aggregates, which can be visualized by microscopy (Figure 1). Fibrils can also fragment and liberate additional seeds, which possess templating (and therefore self-perpetuating) activity of their own. Theoretical considerations [5] indicate that the frangibility (i.e., the intrinsic propensity of fibrils to fragment into smaller units) is a crucial determinant of their self-propagation. A fibril that never breaks would be relatively harmless because it would be unable to maintain the disease-generating process. Substances

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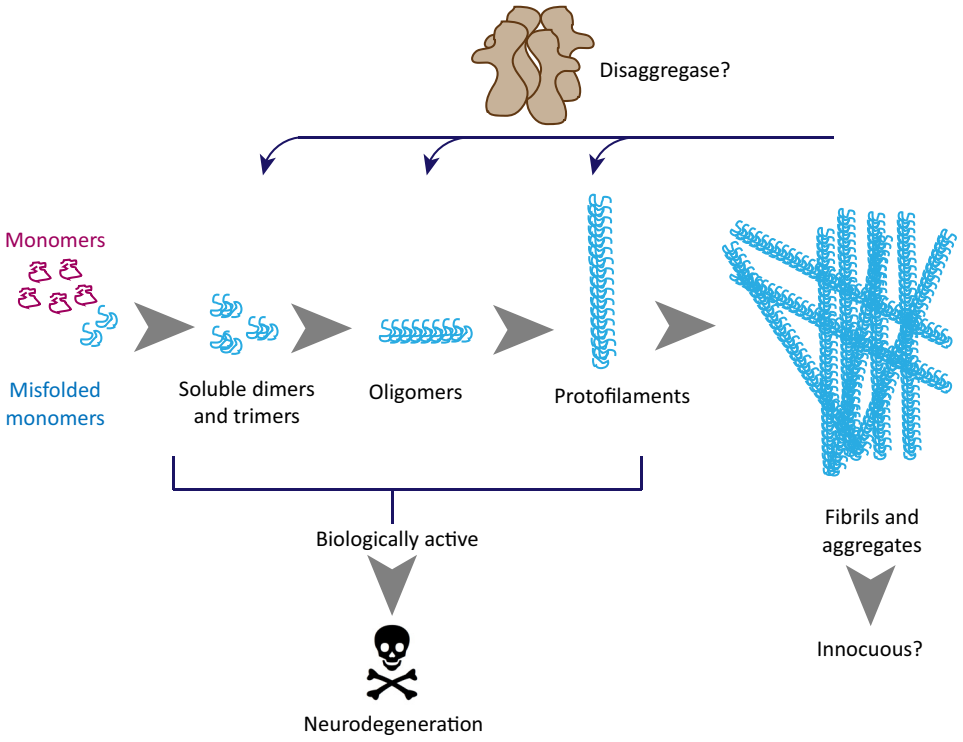

Figure 1. The Life Cycle of Protein Aggregates in Protein Misfolding Disorders (PMDs). The partial unfolding of proteins can result in the formation of abnormally folded soluble dimers and trimers. These can associate with each other or with additional monomers resulting in larger species. Further assembly results in protofilaments, which interact with each other to generate fibrils and larger structures including plaques and tangles. The precise composition of the 'propagon' (i.e., the minimal self-replicating species) is unknown. Likewise, it is unknown whether the toxic species is identical with the propagon. It is often said that large fibrils may be harmless, yet large aggregates exist in equilibrium with oligomeric species and the latter can spawn from the former. Fragmentation of larger aggregates can be spontaneous or catalyzed by disaggregases and liberates further oligomeric species, which can seed further aggregation.

that reduce aggregate frangibility are therapeutic [6,7]. Note, however, that this model of cyclical propagon amplification does not explain the toxicity associated with the deposition of protein aggregates. Indeed, it is compatible with the existence of 'functional amyloids', which may occur physiologically and exert beneficial biological functions [8].

Among the best-characterized PMDs are prion diseases, which result from misfolding and aggregation of cellular prion protein (PrP^{C}) into highly ordered, beta sheet-rich aggregates. By our definition [9], the 'prion' is the agent that causes prion diseases [also called transmissible spongiform encephalopathies (TSEs)]. Crucially, this definition does not assign a specific physical entity to the word 'prion'. Instead, the prion is simply a propagon associated with TSEs. While there is little doubt that the prion comprises primarily a misfolded (and perhaps post-translationally modified) version of PrP^{C}, it can assume various forms ranging from large, insoluble fibrillary aggregates and plaques that resist proteolytic digestion (and are termed PrP^{Sc}) to small, soluble, protease-sensitive oligomers comprising only a few molecules. Because of their higher molar ratio, these oligomers may possess higher biological activity relative to their weight, and >90% of prion infectivity from brain homogenates is typically protease sensitive. Conversely, many methods result in the conversion of recombinant PrP into a protease-resistant form, but this conversion does not necessarily give rise to propagons. These qualifications are essential to understanding prion biology and contradict the common misconception of prions being identical with protease-resistant PrP [10–12].