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Structural studies on the mechanism of protein aggregation in age related neurodegenerative diseases

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ABSTRACT

The progression of many neurodegenerative diseases is assumed to be caused by misfolding of specific characteristic diseases related proteins, resulting in aggregation and fibril formation of these proteins. Protein misfolding associated age related diseases, although different in disease manifestations, share striking similarities. In all cases, one disease protein aggregates and loses its function or additionally shows a toxic gain of function. However, the clear link between these individual amyloid-like protein aggregates and cellular toxicity is often still uncertain. The similar features of protein misfolding and aggregation in this group of proteins, all involved in age related neurodegenerative diseases, results in high interest in characterization of their structural properties. We review here recent findings on structural properties of some age related disease proteins, in the context of their biological importance in disease.

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1. Introduction

Neurodegenerative diseases such as Alzheimer's diseases (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD) share similar histopathological features and have cellular and molecular mechanisms in common. In all these diseases, certain proteins misfold and aggregate, and accumulating protein deposits are pathological hallmarks for the respective disease. In many cases, these aggregated protein have a very ordered structure and exhibit characteristics of so called amyloid-like protein assemblies (Cases, 2001; Sipe and Cohen, 2000; Nelson and Eisenberg, 2006) (Fig.1).

Protein aggregation and amyloid formation research – across a wide range of neurodegenerative diseases – progressed extensively during the last decade. It became clear that, although manifesting differently, many neurodegenerative diseases share two characteristic features, which are the presence of amyloid-like misfolded protein deposits and the loss of neuronal function (Ross and Poirier, 2004).

It is well accepted that the disease symptoms in "amyloid diseases" are associated with the misfolding and aggregation of soluble proteins (Ross and Poirier, 2004; Soto, 2003; Naeem and Fazili, 2011; Tran and Miller, 1999).

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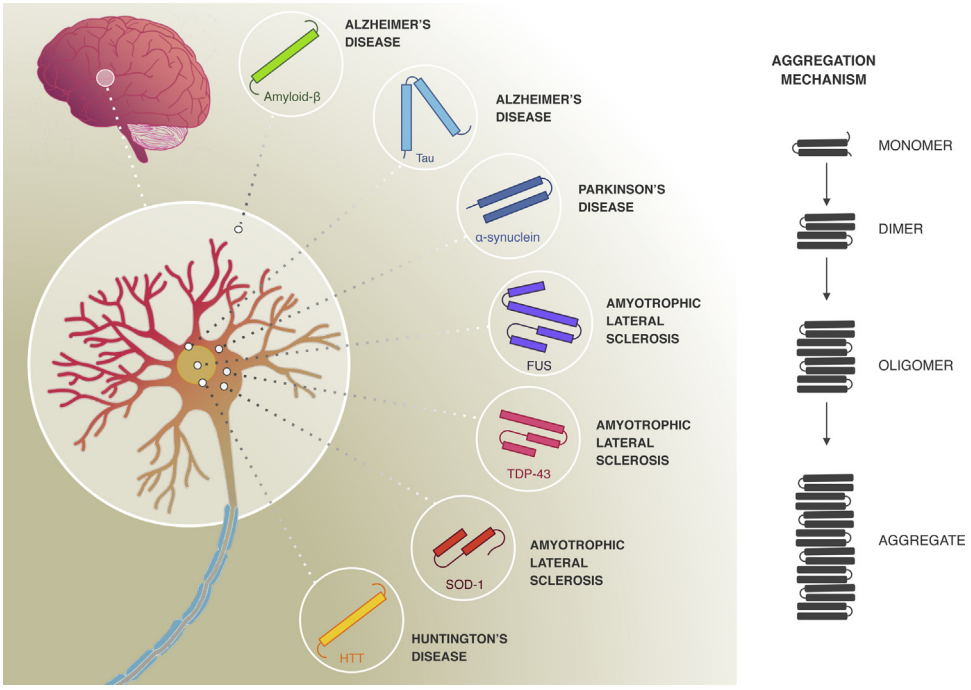

Fig. 1. Protein aggregation in neurodegenerative diseases. In many protein misfolding diseases, natively unfolded monomers form cross β-sheet assemblies, which evolve into oligomers, and finally form highly ordered fibrillar aggregates. This process is associated with neurodegeneration and produces insoluble protein deposits. It is widely believed that these lesions cause cell death, but direct evidence is sparse, and this assumption is controversial (De Calignon, 2010).

Amyloid fibrils resemble thread like protein assemblies composed of β-sheet stacks of protein monomers and/or oligomers (Nelson, 2005; Ono et al., 2009; Sawaya, 2007; Lesné, 2006; Jahn, 2010). The structure and the biophysical properties of amyloid fibrils are very similar across different amyloid diseases, despite the fact that each disease involves the amyloidogenic aggregation of one or several distinct proteins (Naeem and Fazili, 2011; Dobson, 2003, 2004; Baker, 2000). Furthermore, amyloid fibril formation has been reported to be associated with the loss of protein function (Winklhofer et al., 2008; Paine, 2015), a toxic gain of function (Paine, 2015; Rajagopalan and Andersen, 2001; Avila et al., 2010; Cowan and Mudher, 2013; Bretteville and Planel, 2008; Barmada, 2010), or even functional reversible amyloid assembling (Otzen, 2010; Furukawa and Nukina, 2013; Maji, 2008, 2009; Greenwald and Riek, 2010). Using traditional histopathological staining (*e.g.* Thioflavin-T, silver staining), amyloid-like protein aggregates and inclusion bodies can reliably be visualized (Biancalana and Koide, 2010; Jucker and Walker, 2013) but structural information remains obscured. Classic biophysical protein structure techniques, such as X-ray crystallography, Small-angle X-ray scattering (SAX), nuclear magnetic resonance spectroscopy (NMR), Transmission Electron Microscopy (TEM), Circular Dichroism (CD) and Atomic Force Microscopy (AFM) mostly depend on a well-defined protein structure and are limited in their application to multi-protein assemblies and proteins with flexible changing structure (Dyson and Wright, 2005; Uversky, 2011a). In recent years, however, the introduction of new high-resolution microscopy and biophysical techniques – such as Cryo-electron microscopy, super-resolution microscopy, single molecule microscopy, and magnetic resonance spectroscopy – allowed us to identify structural similarities and differences between protein aggregates found in different diseases.

In vitro experiments on different amyloid-forming proteins showed common path of structural transitions: (1) the natively folded protein monomer becomes (partially) unfolded and transit into an unstable disordered molten globule state (Ptitsyn and Uversky, 1994), (2) from where it can adopt an alternative conformation (or misfolded state), which enable the protein to assemble into well-structured, energetically stable amyloid-like multi-protein assemblies. In the last decades, more and more amyloid forming proteins have been identified in different neurodegenerative diseases, many of which classify as intrinsically unfolded (IUPs) or disordered proteins (IDPs). IDPs appear to be very sensitive to misfolding and aggregation, likely because of their already "unfolded" nature (Liu and Huang, 2014; Forman-Kay and Mittag, 2013; Oldfield and Dunker, 2014; Tompa, 2012).

The formation of amyloid structures correlates with cell death in most of the neurodegenerative diseases mentioned. However, it remains unclear if amyloid is directly cell pathogenic or if the process of transition from a natively folded protein into amyloid either reflects, or triggers, the toxic event that ultimately leads to cell death. A detailed analysis of the structural properties and transitions underlying amyloid formation and toxicity is needed to explore the actual role of amyloids per se in protein aggregation diseases.

In this review we introduce the recent findings about structural properties of well-studied amyloid proteins involved in neurodegenerative diseases.

1.1. Intrinsically disordered proteins

Some proteins do not fold into a specific unique secondary and tertiary structure under normal physiological condition but rather stay in a partially folded or unfolded state; or certain stretches in the protein amino acid sequence may fold in presence of specific binding partners (Oldfield and Dunker, 2014).

Based on prediction of disordered protein domains (using *DISORDERED2*) (Ward et al., 2004), long disordered regions (IDRs) are present in 2% of archaebacterial, in 4.2% of eubacterial, and in 33% (!) of eukaryotic proteins (Pavlović-Lažetić, 2011). Such intrinsically disordered proteins (IDPs) are also highly abundant among disease-related proteins, which are often collectively termed "prion-like" proteins, because of their intrinsic property to assemble into