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Protein aggregation and neurodegeneration in prototypical neurodegenerative diseases: Examples of amyloidopathies, tauopathies and synucleinopathies

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ABSTRACT

Alzheimer's and Parkinson's diseases are the most prevalent neurodegenerative diseases that generate important health-related direct and indirect socio-economic costs. They are characterized by severe neuronal losses in several disease-specific brain regions associated with deposits of aggregated proteins. In Alzheimer's disease, β-amyloid peptide-containing plaques and intraneuronal neurofibrillary tangles composed of hyperphosphorylated microtubule-associated protein tau are the two main neuropathological lesions, while Parkinson's disease is defined by the presence of Lewy Bodies that are intraneuronal proteinaceous cytoplasmic inclusions. α-Synuclein has been identified as a major protein component of Lewy Bodies and heavily implicated in the pathogenesis of Parkinson's disease. In the past few years, evidence has emerged to explain how these aggregate-prone proteins can undergo spontaneous self-aggregation, propagate from cell to cell, and mediate neurotoxicity. Current research now indicates that oligomeric forms are probably the toxic species. This article discusses recent progress in the understanding of the pathogenesis of these diseases, with a focus on the underlying mechanisms of protein aggregation, and emphasizes the pathophysiological molecular mechanisms leading to cellular toxicity. Finally, we present the putative direct link between β-amyloid peptide and tau in causing toxicity in Alzheimer's disease as well as α-synuclein in Parkinson's disease, along with some of the most promising therapeutic strategies currently in development for those incurable neurodegenerative disorders.

Abbreviations: Aβ, beta-amyloid peptide; AAV, adeno-associated virus; ABAD, amyloid-beta-binding alcohol dehydrogenase; AD, Alzheimer's disease; ALP, autophagy-lysosome pathways; Apaf-1, apoptic protease-activating factor 1; APP, amyloid precursor protein; AICD, APP intracellular C-terminal domain; α-syn, α-synuclein; BAC, bacterial artificial chromosome; BAD, BCL2-associated agonist of cell death; BAX, BCL2-associated X; CDK5, cyclin-dependent kinase 5; CMA, chaperone-mediated autophagy; CSF, cerebrospinal fluid; DLB, Dementia with Lewy Bodies; EGCG, epi-gallocatechin gallate; ER, endoplasmic reticulum; FTPD-17, frontotemporal dementia with Parkinsonism linked to chromosome 17; GCase, glucocerebrosidase; GSK3β, glycogen synthase kinase 3-beta; IDE, insulin degrading enzyme; LAMP, lysosome-associated membrane protein; LB, Lewy Bodies; LN, Lewy neurites; LRP, LDL receptor-related protein; LOAD, late onset AD; MAM, mitochondrial-associated ER membrane; MEF2D, myocyte enhancer factor 2D; MSA, Multiple System Atrophy; NDRPs, neurodegenerative disease-related proteins; NFTs, neurofibrillary tangles; NMDARs, NMDA-type glutamate receptors; PD, Parkinson's disease; pffs, preformed-fibrils; PHF, paired helical filaments; PrP^{sc}, misfolded prion protein PS1, presenilin 1; PSP, progressive supranuclear palsy; QOL, quality of life; ROS, reactive oxygen species; SF, straight filaments; SNARE, soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor; SNpc, substantia nigra pars compacta; SP, senile plaques; UPS, ubiquitin–proteasome system; TFEB, transcription factor EB; tg, transgenic; TUNEL, Terminal deoxynucleotidyl transferase-dUTP nick end labeling.

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1. Introduction

1.1. Socio-economic aspects

The continuing demographic shift of population toward an older society has led to a growing prevalence of chronic age-related diseases in all industrialized countries. Development of degenerative diseases, such as Alzheimer's disease (AD), associated with neurodegeneration, impaired synaptic function, and massive brain cell loss, loss of cognitive ability and premature death (Holscher, 1998), has a major impact on health along with economical ramifications in Western world. The socioeconomic impact of AD worldwide is immense, even though it is difficult to provide an exact estimation. AD is the fourth main cause of death affecting more than 35 million people worldwide and it is projected to almost quadruple by 2050 (Ferri et al., 2005; Prince et al., 2013a) whereas the number of caregivers will rise up to 216 millions. Furthermore, the direct and indirect economic cost associated with the disease in 2010 was estimated at more than $600 billion worldwide and it is expected to rise at $1 trillion by 2030 (Prince et al., 2014), making AD and other dementias the world's "18th largest economy" (Prince et al., 2013b). The greatest economic cost of dementia is associated with providing institutional and home-based long-term care rather than direct medical services. The prevalence of dementia increases strongly with age and it is projected that the costs of dementia could more than double by 2040 as the nation's population continues to grow older, assuming that the age-specific occurrence rate of the disease remains constant (Prince et al., 2013a). The average lifespan of sufferers is between 7 and 10 years from the time of diagnosis and no cure is presently known.

The pathogenesis of AD has not yet been clarified and the understanding of the disease mechanism remains elusive. Even though the clinical symptoms of AD are usually diagnosed in older people, there are significant evidences indicating that AD-related processes and mechanisms initiate several decades before the clinical onset of the disease (Langbaum et al., 2013). Despite the immense research efforts that have been put over the past years on the characterization of AD and the development of disease-modifying therapeutic approaches, there is still no cure for AD. To date, AD can only be confirmed postmortem whereas initiation of AD pathology is estimated to start several (10–15) years prior to the onset of clinical symptoms. This makes imperative the early identification of AD and the discovery of diagnostic markers for AD (DeKosky and Marek, 2003) key factors for prevention and successful therapeutic intervention of AD. The recent advances in molecular biology, genetics, neurochemistry and imaging technologies (including new amyloid imaging agents) have provided insights of the processes involved in the pathogenesis of AD and have made possible to track amyloid pathology along with disease progression in the living patient.

Parkinson's disease (PD) affects 1.1 million persons in the EU and 6.3 million worldwide (Dowding et al., 2006). Throughout Europe, the annual burden to society including both direct and indirect costs, has been estimated at EUR 138,000 per patient (increasing 5% per year) and these findings are roughly within the same range as estimates from other developed nations (Source: JPND website) (Gammon, 2014). While drug therapy for symptom management makes up the largest portion of direct health care costs (market for drugs to treat PD had a value of EUR 1.8 billion), it accounts for only 10% of total costs as the major costs are consecutive of late stage complications and dramatic impairment of quality of life (QOL) (Dowding et al., 2006). Therefore, neuroprotective or neurorestorative strategies that would stop or slow down the yet unrelenting degenerative process are eagerly awaited as they would have a huge impact both on PD patients' QOL and the economic burden for the society.

1.2. Anatomopathological aspects

AD and PD share striking common features despite diverse clinical symptoms and transmission mode (Bertram and Tanzi, 2005). The hallmarks of these disorders are a selective neuronal vulnerability with degeneration in specific brain regions leading to (i) inexorable impairments of memory and cognitive functions in AD and (ii) paralysis-like syndrome in PD, and deposits of aggregated proteins of aberrant conformation (Taylor et al., 2002). The two neuropathological hallmarks of AD have been described in the original report by Alois Alzheimer (Maurer et al., 1997), as the senile plaques (SP) containing extracellular deposits of beta-amyloid peptide (Aβ), and intraneuronal neurofibrillary tangles (NFTs) composed of abnormal filaments of hyperphosphorylated microtubule-associated tau protein (Serrano-Pozo et al., 2011). Abnormal accumulation of misfolded α-synuclein (α-syn) is the pathological hallmark of several neurodegenerative diseases and forms Lewy Bodies (LB) and neurites (LN) in PD and Dementia with Lewy Bodies (DLB) or glial cytoplasmic inclusions in Multiple System Atrophy (MSA) (Goedert et al., 2013). Most notably, these diseases belong to proteinopathies, defined by the misfolding of a disease-specific protein that self-assembled into an aggregated β-sheet rich structure. Despite considerable differences in primary sequence, the pathological conformers of the disease-specific proteins share similar important structural features. The molecular mechanisms accountable for the transition from a soluble, functional, conformation to an aggregated, pathological, one are not completely understood (Soto, 2003). Quality control pathways protect cells from the deleterious effect of misfolded proteins. Molecular chaperones refold abnormally folded polypeptides or direct them to degradation machinery (Kim et al., 2013). Failure to refold or to degrade aberrant proteins leads to their aggregation (Hipp et al., 2014). Neurons, as postmitotic cells, are particularly sensitive to misfolding injury, as they cannot dilute it by means of cell division. In addition, the accumulation of aberrant proteins increases with age, when quality control might become less efficient, as illustrated both by a decreased activity of the ubiquitin/proteasome system (Dantuma and Bott, 2014) and autophagy (Cuervo and Dice, 2000; Martinez-Vicente and Cuervo, 2007). Impaired proteostasis, in combination with other cellular alterations, is believed to be responsible for the excessive aggregation of misfolded proteins in AD and PD.

The pathogenic roles of Aβ and tau in AD, as well as α-syn in PD are sustained by several lines of evidence. Research over the last twenty years has revealed and clarified the pathological pathways and mechanisms of these diseases. These changes in the disease-specific proteins are also associated with noticeable activation of inflammatory processes and increased levels of oxidative stress, inflammation, and neuronal cell death (Ballard et al., 2011; McGeer and McGeer, 2007). Nevertheless, it is difficult to determine whether the presence of these protein aggregates is rather a consequence rather than a cause. Numerous genetic, cell biology and biochemical data support the model whereby neurodegeneration is caused by a toxic gain of function of the misfolded protein. Even though, the correlation between protein aggregation and nervous system degeneration remains mostly unknown, these disease-specific aggregated proteins and peptides have apparent diagnostic and even therapeutic implications (Ross and Poirier, 2004). In AD, the prevailing hypotheses are centered on the Aβ deposits and NFTs, which have been described in patients with AD (Behl, 1999) while α-syn receives most attention in PD. It is widely considered that abnormal accumulation and aggregation of these disease-specific proteins lead to neurodegeneration; therefore these proteins have been studied extensively in order to understand the ongoing mechanisms and identify potential treatment approaches. In this review, we place these crucial questions into the context of what is

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