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Therapeutic strategies for targeting neurodegenerative protein misfolding disorders

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Neurodegenerative diseases can arise from a multitude of different pathological drivers, however protein misfolding appears to be a common molecular feature central to several disorders. Protein folding, and attainment of correct secondary and tertiary structure, is essential for proper protein function. Protein misfolding gives rise to structural perturbations that can result in loss of protein function or a gain of toxic function, such as through aggregation, either of which can initiate and propagate biological responses that are deleterious to cells. Several neurodegenerative diseases, such as Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease and Parkinson's disease, each have identified molecular components in which protein misfolding perturbs cellular systems that ultimately lead to cell death, and this predominately occurs in neurons. Current efforts focused on developing therapies for protein misfolding disorders have employed diverse strategies; inhibiting the production of disease-relevant proteins prone to misfolding, inhibiting the aggregation of misfolded proteins, removing and preventing spread of aggregated misfolded proteins and manipulating cellular systems to mitigate the toxic effects of misfolded proteins. Each of these strategies has yielded therapeutic agents that have transitioned from preclinical proof of concept studies into human clinical testing. These approaches and therapies are described herein.

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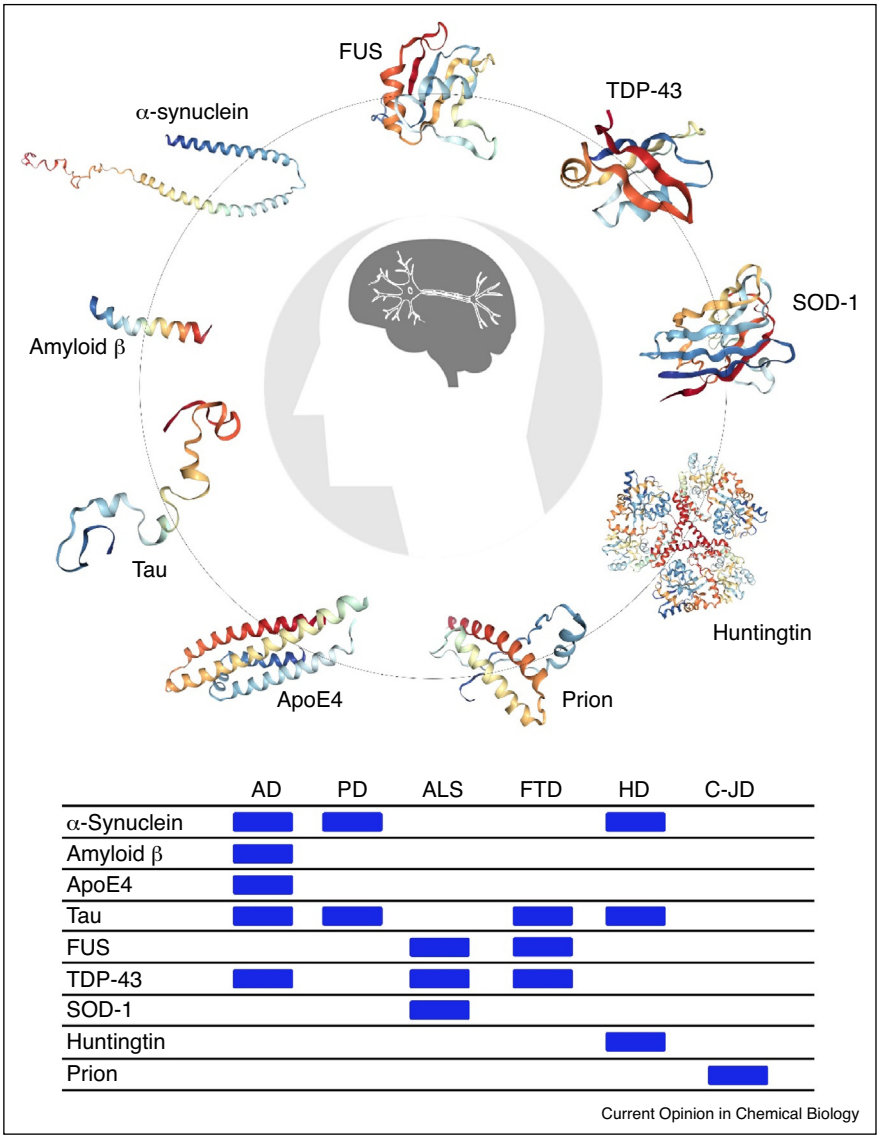
Introduction to neurodegenerative protein misfolding diseases

Medical and health care advances over the past century have driven an approximate 30-year increase in human life expectancy, resulting in the emergence of an aging population living into their eighth and ninth decades [1]. In parallel with increased longevity, there has been a corresponding increase in the prevalence of neurodegenerative diseases [2], many of which are progressive and irreversibly develop over several decades. Despite the many scientific advances providing insights into the molecular drivers of pathology, neurodegenerative disease remains an area of high unmet medical need. For some disorders symptomatic therapies exist that can confer limited benefits, however there are no approved disease modifying therapies that can stave off the disease progression and terminal outcomes that are devastating for patients and their families. Although there are myriad genetic and environmental factors that influence the risk of developing neurodegenerative disease and the rate of disease progression, protein misfolding and accumulation of aggregates is a common pathological event at the core of several of these debilitating disorders. In some cases, individual misfolded proteins are linked to distinct neurodegenerative disorders, however multiple proteinopathies can also occur within a single disease domain (Figure 1).

Alzheimer's disease (AD) is the most common cause of dementia in aged patients [3]. Two hallmark pathological substrates are associated with AD, amyloid plaques and neurofibrillary tangles, and these are implicated in the neuronal loss and brain atrophy which underlie the primary symptoms of memory and language loss, impairment in visuospatial and executive function and behavioral abnormalities. Amyloid plaques are deposits of aggregated amyloid beta peptides (amyloid β, Aβ), which are protein fragments derived from the proteolytic processing of the amyloid precursor protein (APP) by beta-site APP cleaving enzyme 1 (BACE1) and gamma secretase (γ-secretase). Aβ peptides can adopt soluble folded structures, but can transition into higher order misfolded and aggregated states of oligomers and fibrils and plaques [4]. Human genetic studies link Aβ to risk of developing AD, in which mutations that enhance plaque formation are associated with aggressive forms of AD and mutations that reduce Aβ production and aggregation are protective [5,6]. These data support the amyloid hypothesis of AD that Aβ pathology is causative for disease initiation and progression.

Neurofibrillary tangles are composed of insoluble, aggregated and hyperphosphorylatedi microtubule associated protein tau (MAPT, tau). Mutations and other genetic and environmental cues can promote tau hyperphosphorylation, which results in tau dissociation from

Figure 1



Misfolded proteins commonly involved in neurodegenerative disease. Graphic illustration of the myriad proteins prone to misfolding and aggregation that have been linked to the development and progression of neurodegenerative disease. Representative structures have been copied from the Protein Data Bank (PBD). For each indicated proteinopathy, the PDB ID is provided: Abeta (1AMB), tau (2M27), a-synuclein (1XQ8), ApoE4 (1B68), FUS (2LA6), TDP-43 (3D2W), SOD1 (3CQQ), Huntingtin (3IOR), and Prion (1QLX). Lower graphic illustrates in which of the indicated neurodegenerative disorders the indicated proteinopathy has been documented. A blue box indicates positive association between protein and disease.

microtubules and promotes formation of proto-fibrils and aggregates [7]. Tau-dependent destabilization of the microtubule transport network combined with accumulating neurofibrillary tangles are thought to ultimately contribute to neuronal dysfunction and cell death. Cortical neurofibrillary tangle burden correlates with the severity of cognitive impairment in AD, indicating tau pathology is directly linked with clinical disability [8].

Parkinson's disease (PD) is progressive motor disorder arising from a selective degeneration of dopaminergic neurons in the substantia nigra that project into the striatum, and is the second most common age-related neurodegenerative disorder [3]. Loss of basal ganglia neurons deteriorates motor control, causing rigidity, tremor, bradykinesia, akinesia and impaired gait and balance [9]. PD patients can also develop dementia and cognitive impairment [10]. Neuronal Lewy bodies are the primary pathologic feature of PD, which are aggregates primarily of misfolded α-synuclein [11]. Prior to Lewy body formation, soluble misfolded α-synuclein may have toxic effects in mediating mitochondrial,