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Prion-like transmission of pathogenic protein aggregates in genetic models of neurodegenerative disease

Margaret MP Pearce

A key pathological hallmark of most neurodegenerative diseases is the misfolding of a particular protein, leading to deposition of toxic protein aggregates in brain tissue. Recent data provide compelling evidence that pathogenic protein aggregates have prion-like properties—they self-replicate by templated misfolding of monomeric proteins and spread between individual cells. Studies in genetic model organisms have expanded our understanding of how prion-like pathogenic aggregates propagate *in vivo*, revealing potential roles for spreading along neural networks and key cellular processes in both neurons and glial cells. These findings and future studies in genetic models will help guide the development of novel therapeutic strategies that directly target the molecular mechanisms underlying these devastating diseases.

Address
Department of Biological Sciences, University of the Sciences, Philadelphia, PA 19104, USA

Corresponding author: Pearce, Margaret MP (m.pearce@usciences.edu)

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Introduction

With our world's population aging at an unprecedented rate, age-associated illnesses such as neurodegenerative diseases [*e.g.*, Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD)] are increasing in prevalence. These incurable disorders are characterized by the progressive loss of neurons, leading to a variety of neurological symptoms such as memory loss, cognitive decline, and motor dysfunction. An underlying feature shared by nearly all neurodegenerative diseases is the misfolding of certain proteins (Table 1), leading to the formation of stable amyloid aggregates inside or outside neurons and glia [1]. The specific event(s) that trigger protein misfolding and aggregation in each disease are not completely understood. However, the capacity of cells to maintain protein homeostasis (*i.e.*, 'proteostasis') is likely compromised by aging or certain genetic mutations [1].

A growing body of evidence supports the hypothesis that neurodegenerative disease-associated protein aggregates propagate through the brain with similarities to infectious prions (Table 1) [2]. Speculation about this began in the 1980s with the discovery by Prusiner and colleagues of protein-only infectious agents ('prions') that cause transmissible spongiform encephalopathies [3]. In these diseases, amyloid aggregates form due to misfolding and aggregation of prion protein (PrP) and spread to other cells or organisms via templated conformational change of normally-folded PrP molecules (Figure 1). The idea that prion-like mechanisms could be expanded to more common neurodegenerative disorders was first hinted at by staging of AD, PD, and ALS patient brains, revealing unique but stereotypical patterns of spread between anatomically-connected brain regions [4–6]. Numerous studies have since demonstrated prion-like behavior for pathological Aβ, tau, α-synuclein, SOD1, TDP-43, and mutant huntingtin (Htt) proteins (Table 1), though there is no evidence that these protein aggregates are truly infectious between organisms as bona fide prions are. Most of these studies have involved supplementing the media bathing cultured cells with exogenous aggregates and monitoring aggregate entry into the cytoplasm [7–13]. However, aggregates were typically added to the cells at concentrations considerably higher than would likely be observed in the disease state. Thus, genetic animal models of neurodegenerative disease have provided an opportunity to investigate prion-like mechanisms under more physiological conditions. In this review, I summarize recent data that support prion-like transmission of pathogenic aggregates *in vivo* and discuss emerging concepts for how spreading could occur in the intact central nervous system (CNS).

Genetic models of AD and other tauopathies

Two types of proteinaceous lesions serve as histopathological markers of AD—extracellular Aβ plaques and intracellular neurofibrillary tangles (NFTs) [14]. Aβ plaques form following proteolytic cleavage of amyloid precursor protein (APP), and NFTs result from misfolding of hyperphosphorylated tau/MAPT, a

Table 1

***In vivo* models demonstrating prion-like transmission of protein aggregates associated with the most common neurodegenerative diseases**

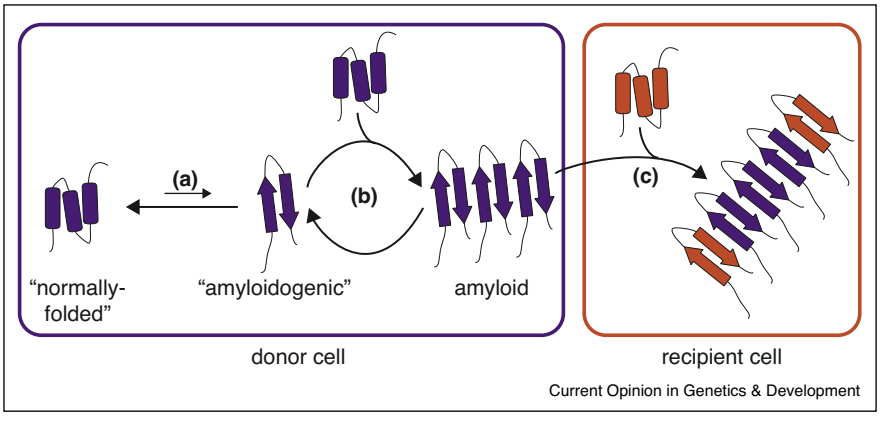
Disease(s)	Aggregating protein	Mammalian models	Invertebrate models
Alzheimer's disease	Aβ	Spread along anatomical tracts in marmosets [16] or mice [17–22] injected with AD brain homogenates Spread from subiculum to synaptically-connected regions in APP(E593G) 'Arctic mutant' mouse [25]	n.a.
Alzheimer's disease and tauopathies	Tau	Fibrillar tau injected into transgenic-tau mouse brains spreads along neural tracts [23,24] Possible spread of tau from entorhinal cortex to dentate gyrus in hTau-P301L mouse [26,27]	n.a.
Parkinson's disease and synucleinopathies	α-Synuclein	Fibrillar α-synuclein injected into wild-type or α-synuclein-transgenic mice results in pathology spreading through CNS along anatomical tracts [32–34,35•]	*C. elegans*: transfer between pharyngeal muscle cells and neurons, mediated by dynamin [36•]
Amyotrophic lateral sclerosis	SOD1	Spinal cord homogenates injected into sciatic nerve spread rostrally up spinal cord into synaptically-connected brain regions [37•]	n.a.
Huntington's disease	Huntingtin	Transfer from R6/2 mouse brains to human neurons; can be blocked by botulinum toxin [42] Transfer from human-derived fibroblasts or iPSCs into wild-type mouse brains [43]	*Drosophila*: spread of mutant Htt along unique paths depending on originating neurons, requires exocytic machinery [46••] *Drosophila*: spread from neurons to glia, requires glial phagocytic machinery [47••]

Neurodegenerative diseases that most commonly afflict humans are listed, and the protein that misfolds and aggregates ('aggregating protein') in each disease is indicated. Studies involving mammalian or invertebrate models that have demonstrated prion-like spreading of pathogenic protein aggregates *in vivo* are described. Corresponding references are indicated in brackets.

microtubule-stabilizing protein. The presence of Aβ plaques and NFTs confirms post-mortem diagnosis of AD, but NFTs are also characteristic of other diseases collectively known as tauopathies. The vast majority of AD cases are idiopathic, although rare inherited mutations in APP, the enzymes that process APP, or tau can cause early-onset AD and tauopathies. Aβ plaques and NFTs follow distinct spreading patterns in AD patient brains [15], suggesting that different populations of neurons are selectively vulnerable to aggregation of Aβ vs. tau.

Aggregate assemblies of Aβ or tau spread after focal injection of either purified fibrils or diseased brain

Figure 1



Molecular mechanisms of prion-like transmission of protein aggregates.
Normally-folded proteins can assume a misfolded, β-sheet-rich, amyloidogenic conformation due to rare spontaneous, acquired, or inherited changes in protein structure **(a)**. Once formed, amyloidogenic proteins template the conversion of normally-folded versions of the same protein, causing growth of a stable amyloid fibril **(b)**. Amyloid 'seeds' can then spread to other cells by physically transferring out of 'donor cells' and templating the conformational change of normally-folded proteins in 'recipient cells' **(c)**.