Brain degeneration linked to "fatal attractions" of proteins in Alzheimer's disease and related disorders

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A common mechanistic theme shared by Alzheimer's disease (AD) and many other seemingly unrelated neurodegenerative disorders is emerging from accelerating research progress in the last few years which is beginning to dispel the pessimistic assumption that each phenotypically and genotypically distinct sporadic as well as hereditary degenerative disorder of the aging central nervous system (CNS) will require a different, disease-specific therapeutic intervention. (For reviews, see the Center for Neurodegenerative Disease Research website at http://www.med.upenn.edu/cndr, and [1–3] here.) Specifically, a growing body of data from different lines of investigation has made it increasingly clear that a large number of diverse neuropsychiatric degenerative disorders are characterized neuropathologically by intracellular and/or extracellular filamentous lesions and that these lesions are implicated mechanistically in the onset/progression of disease in affected patients. Accordingly, it has become compellingly plausible to postulate that these disorders may share similar targets for drug discovery, despite differences in the molecular composition of their disease specific filamentous lesions and the diverse cell types and brain regions in which the lesions accumulate (see Table 1). For example, we have proposed that the onset and/or progression of brain degeneration in AD and other neurodegenerative disorders is initiated by abnormal interactions ("fatal attractions") between brain proteins that lead to their assembly into filaments and the aggregation of these filaments as fibrous intracytoplasmic inclusions or extracellular plaque deposits in the diseased brain.

Examples of some of the most well characterized of these filamentous lesions are summarized in Table 1 and they are exemplified by the: 1) Intranuclear neuronal inclusions formed by diverse proteins harboring mutant or abnormally expanded polyglutamine tracts in hereditary trinucleotide repeat disorders; 2) Intracytoplasmic neurofibrillary tangles (NFTs) and extracellular amyloid or senile plaques (SPs) in sporadic AD and familial AD (FAD); 3) Prion protein deposits in sporadic or genetic forms of spongiform encephalopathy; 4) Intraneuronal Lewy bodies (LBs) in non-familial and familial Parkinson's disease (PD) (see Table 1 and [1–3]). Despite the fact that almost all of these filamentous brain lesions are diagnostic of specific disorders, there are well known instances in which these pathologies occur in more than one seemingly distinct neurodegenerative disease, and this is exemplified most clearly by the enigmatic overlap between the neuropathology of classic AD and classic PD.

Indeed, the heterogeneous group of dementing disorders that are classified as AD based on the presence of abundant SPs and NFTs according to current consensus criteria, overlap with diverse neurodegenerative tauopathies characterized by prominent tau-rich fibrillary brain tangles, and the synucleinopathy brain disorders characterized by large accumulations of synuclein lesions [1,3]. Notably, although the diagnostic hallmarks of AD are numerous SPs composed primarily of Aβ fibrils and intraneuronal NFTs formed by filamentous hyperphosphorylated tau, AD NFTs are similar to the filamentous tau inclusions that are the defining lesions of neurodegenerative tauopathies, most of which do not exhibit any other disease specific brain lesions. Moreover, the discovery of multiple tau gene mutations that are pathogenic for familial frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-

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Table 1
Fatal protein attractions in neurodegenerative diseases

Disease	Lesion/Protein
AD	Plaques/Amyloid-beta
	Tangles/Tau
DS	Plaques/Amyloid-beta
	Tangles/Tau
	Lewy Bodies/Alpha-synuclein
	Lewy Neurites/Alpha-synuclein
LBVAD (AD + DLB)	Plaques/Amyloid-beta
	Tangles/Tau
	Lewy Bodies/Alpha-synuclein
	Lewy Neurites/Alpha-synuclein
PD	Lewy Bodies/Alpha-synuclein
	Lewy Neurites/Alpha-synuclein
	Neurites/Alpha-, Beta-synuclein
	Axonal Spheroids/Gamma-synuclein
DLB	Lewy Bodies/Alpha-synuclein
	Lewy Neurites/Alpha-synuclein
	Neurites/Alpha-, Beta-synuclein
	Axonal Spheroids/Gamma-synuclein
MSA	Glial Inclusions/Alpha-synuclein
NBIA 1	Lewy Bodies/Alpha-synuclein
	Lewy Neurites/Alpha-synuclein
	Glial Inclusions/Alpha-synuclein
PSP/CBD	Tangles/Tau
Pick's Disease	Tangles/Tau
FTDP-17	Tangles/Tau
ALS	Axonal Spheroids/Neurofilaments, SOD1
Trinucleotide Repeat Diseases	Nuclear Inclusions/Polyglutamine Tracts
NIID	Nuclear Inclusions/Polyglutamine Tracts
Prion Diseases	Plaques/Prions

This table lists representative examples of neurodegenerative diseases characterized by filamentous protein aggregates discussed here. Abbreviations other than those introduced in the text are: PSP = progressive supranuclear palsy; CBD = corticobasal degeneration; ALS = amyotrophic lateral sclerosis; NIID = neuronal intranuclear inclusion disease.

17) in many kindreds, some of which were thought to have FAD earlier, provided unequivocal proof that tau abnormalities cause neurodegenerative disease in the absence amyloid plaques or any other brain pathology [1,3]. On the other hand, although LBs are the diagnostic hallmark intraneuronal inclusions of PD, they also occur in the most common subtype of AD known as the LB variant of AD (LBVAD), and numerous cortical LBs are the defining brain lesions of dementia with LBs (DLB), which is similar to AD clinically, but distinct from AD pathologically [1,3]. Further, alpha-synuclein gene mutations cause familial PD in rare kindreds, and these mutations may be pathogenic by altering the functions or properties of these synaptic proteins thereby promoting the formation of alpha-synuclein filaments that aggregate into LBs. However, it is now known that FAD mutations and trisomy 21, which causes Down's syndrome, lead to abundant accumulations of LBs composed of alpha-synuclein filaments in the brains of most FAD patients and elderly Down's syndrome (DS) individuals. Indeed, the accumulation of alpha-synuclein into filamentous inclusions appears to play a mechanistic role in the pathogenesis of a number of progressive neurological disorders including PD, DLB, DS, FAD, LBVAD, sporadic AD, multiple system atrophy (MSA), neurodegeneration with brain iron accumulation type 1 (NBIA 1, which was formerly known as Hallervorden-Spatz disease) and other synucleinopathies. This notwithstanding, the explanation for this enigmatic co-occurrence of LBs with NFTs and SPs in diseases caused by abnormalities in genes that are unrelated to the alpha-synuclein gene is completely unclear at this time, and it seems unlikely that brain accumulations of Aβ, tau and synuclein filaments can be accounted for by mutation dependent alterations in levels of brain Aβ alone in FAD.

Nonetheless, the aggregation of brain proteins into potentially toxic lesions is increasingly supported by emerging data as a common mechanistic theme in a di-

verse group of neurodegenerative diseases that share an enigmatic symmetry, i.e. mutations in the gene encoding the disease protein cause a familial brain disorder as well as the hallmark neuropathology of the disorder, but the same brain lesions also form by the corresponding wild type brain protein in sporadic variants of the disease [1,2]. In view of these striking parallelisms between many neurodegenerative diseases, clarification of this enigmatic symmetry in any one of these disorders is likely to have a profound impact on understanding the mechanisms that underlie all of these disorders as well as on efforts to develop novel therapies to treat them. For example, compounds have been identified that prevent the conversion of normal proteins into abnormal conformers with structural properties that predispose the pathological proteins to form potentially toxic filamentous aggregates [5], and it is plausible that some of these agents may have therapeutic efficacy in more than one disorder. Moreover, novel therapeutic interventions based on the use of the peptide building blocks of the abnormal fibrils in AD amyloid plaques as vaccines to prevent or reverse AD amyloidosis [5] could be extended to treat other of the disorders reviewed here. Thus, we predict that as the full implications of insights into abnormal protein-protein interactions or "fatal attractions" coalesce into a fuller understanding of neurodegenerative diseases, they will enhance the likelihood that the next few decades will bring effective treatments for AD and other devastating neurodegenerative disorders caused by abnormal filamentous protein aggregates.

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