Alzheimer’s Disease: The Case for a Paradigm Shift

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Abstract

The widely accepted notion that the insoluble fraction of proteins, once in their cross-beta conformation (amyloid) at the end of the process of aggregation, drives neurodegeneration has been challenged by recent work. Data from a range of different experiments contradict the presumed neurotoxicity of aggregated protein. While the clinico-pathologic model that has defined neurodegenerative diseases for over a century has proven helpful for the development of symptomatic therapies, it has not yielded a single success in disease modification. Biomarker programs inspired in this model have yielded biomarkers of convergence, present in most but pathogenically irrelevant at the individual level. We will discuss opposing hypotheses around which neurodegeneration is classified and approached: gain- versus loss-of-function hypothesis. With evidence from biophysics and genetics, we propose that the loss of proteins in their soluble, monomeric state (proteinopenia) is a more relevant causal factor than their presumed "toxic" accumulation in an amyloid state (proteinopathy): proteins can only function when normal, and cease to function when abnormal. We outline a new approach to neurodegeneration with dual but complementary strategies for disease modification, namely rescue medicine (soluble protein replacement, a universal approach) as a precursor for future deployment of precision medicine (matching molecular interventions to biologically-suitable individuals, an individualized approach). The lessons are primarily drawn from Alzheimer’s disease literature but the implications are extensive to other neurodegenerative disorders.

Keywords

Alzheimer’s disease, proteinopathy, proteinopenia, loss-of-function, Aβ hypothesis

References