Ten Challenges of the Amyloid Hypothesis of Alzheimer's Disease

The inability to effectively halt or cure Alzheimer's disease (AD), exacerbated by the recent failures of high-profile clinical trials, emphasizes the urgent need to understand the complex biochemistry of this major neurodegenerative disease. In this paper, ten central, current challenges of the major paradigm in the field, the amyloid hypothesis, are sharply formulated. These challenges together show that new approaches are necessary that address data heterogeneity, increase focus on the proteome level, use available human patient data more actively, account for the aging phenotype as a background model of the disease, unify our understanding of the interplay between genetic and non-genetic risk factors, and combine into one framework both the familial and sporadic forms of the disease.