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Beyond the "Amyloid Hypothesis"? Rescuing proteostasis in Alzheimer's Disease"

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Alzheimer's Disease (AD) is the most common form of dementia in the elderly population. The estimated global prevalence of AD in 2015 was 46 million with an incidence rate in 2050 of 131 million. In the absence of medical advancements to prevent, slow down, or stop the disease, there will be dramatic effects on society, global health, and economy. AD is characterized by an abnormal accumulation of Aβ amyloid plaques in the brain. The idea that amyloid Aβ peptide aggregation into amyloid fibrils is an important factor in AD development (Amyloid Hypothesis) is supported by a considerable body of evidence. However, the failure of clinical trials for molecules targeting Aβ misfolding and self-assembly points to the need for a deeper comprehension of the mechanisms behind the impaired proteome maintenance occurring in AD.
Here I propose a brief survey on the intertwined biochemical mechanisms that control Aβ homeostasis (proteostasis) by employing an interdisciplinary approach to screen small molecules (e.g. natural compounds, bioconjugates, and repurposed drugs) for their ability to restore physiological Aβ homeostasis by a multitarget strategy. This research activity spans from fundamental topics related to protein/lipid membrane stability, amyloid aggregation, proteasome activation and ligand protein interactions to applications in medicinal chemistry focusing on the development of bioactive compounds as drug candidates in AD therapy.

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