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A One-Drug Strategy is Needed to Attenuate the Multi-Proteinopathy that Leads to Age-Related Diseases

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Introduction

Alzheimer's disease (AD), frontotemporal dementia (FTD), and amyotrophic lateral sclerosis (ALS) are age-related protein accumulation disorders. They exhibit multi-proteinopathy involving tau and TAR DNA-binding protein 43 (TDP43), and the latter two disorders can also accumulate fused in sarcoma protein (FUS). AD is the most common multi-proteinopathy with an additional and perhaps key pathogenic contributor being the Aβ42 peptide. AD can also exhibit the accumulation of α-synuclein, a key protein that accumulates in Parkinson's disease (PD) and related Lewy body diseases. The specific disorders that constitute FTD have a high proportion of familial or inherited cases, whereas less than 5% of AD cases and 5-10% of ALS cases are the familial inherited form, and the cause of the remaining 90-95% of sporadic AD and ALS cases is not fully understood. Many of the molecular and cellular features related to combinations of protein accumulation events are observed in both sporadic and familial forms of these disorders, often occurring for many years before symptoms arise. The multiple protein accumulation/aggregation events may elicit separate degenerative pathways in distinct age-dependent manners, culminating with the enhanced risk of developing one of several protein accumulation disorders (AD, FTD, ALS, PD, Huntington's disease, multiple system atrophy, multisystem proteinopathy).

Potential drugs that only target one type of pathogenic accumulation event (Aβ42) have failed in recent human trials for AD. Thus it is becoming apparent that waiting for individual therapeutics against Aβ42, tau, TDP43, and α-synuclein, to allow for a combination treatment of the multi-proteinopathy in AD, is not a hopeful outlook. ALS and FTD may also need a drug that prevents FUS accumulation and its recruitment of other proteins into aggregates. A single drug development strategy is needed that can counteract the slow clearance common among the listed proteins. Strategies to enhance clearance of multiple types of proteins are guiding efforts to find new drug targets. The autophagy–lysosomal system is a logical target since lysosomes are a primary site for protein clearance in cells.

The lysosomal pathway is critical for cellular homeostasis, providing efficient digestion and turnover of proteins, and contributing to cell health and perhaps longevity as well [1]. The lysosomal enzyme cathepsin B was discovered to degrade Aβ42 through carboxy-terminal truncation [2], and positive cathepsin B modulation effectively reduced pathogenic Aβ assemblies and ameliorated synaptic and behavioral deficits in AD mouse models [2-5]. Currently, enhancing the autophagy-lysosomal pathway of protein clearance is becoming widely accepted as a plausible treatment avenue for many indications, including CNS, metabolic, inflammatory, infectious, and muscle disorders [5-10]. Regarding the treatment of multi-proteinopathy, small-molecule cathepsin B modulators not only reduce intracellular Aβ, and consequently extracellular Aβ levels, they also reduce pathogenic forms of tau, and for both Aβ and tau, their enhanced clearance was associated with recovery of synaptic proteins [11,12]. In addition, an 18-residue peptide that promotesthe lysosomal degradation pathway of autophagy was found to enhance clearance of polyglutamine aggregates related to Huntington's disease [13]. These studies indicate the progress in finding a single target that enhances autophagy–lysosomal efficiency, thereby promoting clearance of those proteins implicated in multi-proteinopathies. Such a target is critical for developing a treatment to slow the onset and/or progression of age-related protein accumulation disorders.

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