A Single Pathway Targets Several Health Challenges of the Elderly

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Abstract

New avenues to modulate the autophagy–lysosomal route of protein clearance have the potential to help treat several disease states to which the elderly are particularly vulnerable. Two recent papers identified distinct ways to tap into the lysosomal degradation pathway of autophagy to reduce age-related protein accumulation events. Shoji-Kawata et al. (Nature 2013;494:201–206) describe a new autophagy-inducing peptide, Tat-Beclin 1, that enhances the clearance of polyglutamine aggregates related to Huntington’s disease and, interestingly, suppresses viral and bacterial infections. Savolainen et al. (Neurobiol Dis 2014;68:1–15) describe a prolyl oligopeptidase inhibitor that reduces α-synuclein species related to Parkinson’s disease and other α-synucleinopathies, and this inhibitor caused a concomitant increase in autophagic activation markers. Previous studies have also linked the autophagy–lysosomal pathway to the protective clearing of the Aβ peptides of Alzheimer’s disease and tau species of tauopathies. Enhancing autophagy–lysosomal efficiency may provide a therapeutic avenue for diverse types of proteinopathies, including the most common neurodegenerative disorders of the elderly.

Introduction

The lysosomal degradation pathway of autophagy is critical for cellular homeostasis, providing efficient digestion and turnover of cellular components and contributing to cell health and longevity. The lysosome organelle contains 50–60 different enzymes responsible for the recycling of cellular constituents and waste, thus employing several degradation avenues to break down biomolecules, including proteins, polysaccharides, lipids, and nucleic acids. Disruption and instability of lysosomes during aging are factors in pathogenic accumulation events, and modulation of the autophagy–lysosomal pathway has been identified as a potential strategy to treat age-related protein accumulation disorders linked to dementia. In addition to neurodegenerative diseases, the lysosomal degradation pathway of autophagy represents a therapeutic target for treating metabolic, inflammatory, infectious, neoplastic, and muscle disorders. Agents that positively influence this single pathway thereby have the potential to offset numerous disease states to which the elderly are particularly vulnerable (results from references 6–20 are summarized in Table 1). Improving the pathway’s function of protein clearance may very well impact human health on a global scale.

Eukaryotic cells have two major intracellular protein degradation pathways, the ubiquitin–proteasome system and the autophagy–lysosomal route. A growing number of target identification and drug discovery efforts point to the latter as a treatment avenue for a broad range of pathologies. The autophagy–lysosomal pathway has a crucial role in cellular defense and cytoplasmic homeostasis, exemplified by a newly identified autophagy-inducing peptide, Tat-Beclin 1. The recent report by Shoji-Kawata et al. is of particular note due to the several disease indications studied. In the report, the Tat-Beclin 1 peptide was found to protect against viral infections, decreasing the replication of several viral pathogens including human immunodeficiency virus (HIV), and even reducing the mortality rate in mice infected with the West Nile virus. They also showed that the lysosomal degradation pathway of autophagy can be induced to defend against a bacterial infection. Specifically, Tat-Beclin 1 reduced the intracellular survival of the bacterium Listeria monocytogenes that causes listeriosis, a disease that produces central nervous system (CNS) infections primarily in the elderly and other at-risk groups (newborns, pregnant women, adults with weakened immune systems). Tat-Beclin 1 was also found to elicit clearance of small polyglutamine (polyQ) aggregates. Thus, the autophagy–lysosomal pathway impacts protein misfolding/accumulation events of polyQ repeat expansion disorders, Huntington’s disease being the most prevalent of the neurodegenerative polyQ disorders.
Intracellular Aβ PolyQ aggregates Clearance of polyQ aggregates Long-lived polyQ aggregates

Bacterial infection Reduced intracellular survival —

Viral infection Reduced mortality of infected mice —

Extracellular Aβ less pathogenic peptides via carboxy-terminal truncation. 7

crossing CatB

The study also found that genetic ablation of CatB, by

catalyzed by the enzyme activity

clearance, and

mutations10,11 or wild-type hAPP.12

b cathepsin modulatory compound that selectively enhances

clearance, and

parameters. Correspondingly, Aβ deposition in mouse models

of Alzheimer’s disease was significantly reduced when

catalyzed by the enzyme activity

clearance, and

mutations in

tau, PHF-tau aggregates, and tau-related pathology occurred

when CatB was enhanced with the modulatory compound

PADK.16,17

Aggregated α-synuclein in dementia with Lewy bodies, Parkinson’s disease, and other α-synucleinopathies is the fourth type of age-related protein accumulation event included as being targeted by the autophagy–lysosomal pathway. In recent studies, α-synuclein was localized to the lysosomal degradation pathway and, similar to Aβ and phosphorylated tau, inhibition of cathepsin proteases caused an increase in α-synuclein aggregates.18,19

Finally, a more recent study by Savolainen et al.20 discovered a link between enhancement of the autophagic pathway and accelerated clearance of α-synuclein. The study identified a compound (KYP-2047) that reduces the amount of aggregated α-synuclein in cellular models and transgenic mice. KYP-2047 positively modulates the lysosomal degradation pathway of autophagy by inhibiting prolyl oligopeptidase, a mechanism distinct from the way Tat-Beclin 1 induces autophagic clearance of polyQ aggregates. Tat-Beclin 1 contains amino acids 267–284 of Beclin 1, an essential autophagy protein in the class III phosphatidylinositol-3-OH kinase complex. By mimicking Beclin 1, the Tat-Beclin 1 peptide blocks HIV-1 Nef’s ability to be an anti-autophagic maturation factor through its interaction with Beclin 1. The recent reports indicate that different mechanistic routes can promote the autophagy–lysosomal pathway to enhance protein clearance.
The autophagy–lysosomal route for protein clearance influences a wide range of disease states, a range that has been further broadened by recent studies. In addition to reducing serious infections commonly found in the elderly, enhancing protein clearance efficiency in cells has the potential to protect against the most common nervous system disorders of the elderly. Over 400 million baby boomers are contemplating the imbalances between protein production and protein clearance that increase their risk for protein accumulation diseases as they age. A single pathway that can target multiple types of proteinopathies provides an optimistic strategy for extending the healthy life span of the aging human population.

Author Disclosure Statement

Dr. Bahr is listed as inventor on awarded patents and recent patent applications covering various compounds, including positive cathepsin modulators, for the treatment of dementia, mild cognitive impairment, traumatic brain injury, neurodegeneration, cardiomyopathies, and eye diseases.

References


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