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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.[1,2] In addition to neurodegenerative diseases, the lysosomal degradation pathway of autophagy represents a therapeutic target for treating metabolic, inflammatory, infectious, neoplastic, and muscle disorders.[3–5] 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.[6] 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.

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Table 1. Effects on Health Challenges of the Elderly When the Autophagic–Lysosomal Route for Protein Clearance Is Enhanced Versus Disrupted

Health challenge	*Effect of enhancing the lysosomal degradation pathway of autophagy*	*Effect of disrupting lysosomal enzyme activity*
Viral infection	Reduced mortality of infected mice	—
Bacterial infection	Reduced intracellular survival	—
PolyQ aggregates	Clearance of polyQ aggregates	Long-lived polyQ aggregates
Mutant huntingtin protein	Neuroprotection	Increased toxicity
Intracellular Aβ	Reduced Aβ levels	Increased Aβ levels
Extracellular Aβ	Reduced Aβ deposits	Increased Aβ deposition
PHF-tau	Reduced PHF-tau	Increased PHF-tau
α-synuclein aggregates	Reduced α-synuclein	Increased α-synuclein aggregates

PolyQ, polyglutamine; PHF, paired helical filament.

Related to the Shoji-Kawata et al. study with regard to the expanding role of autophagy and lysosomes, the pathway also targets proteins associated with other neurodegenerative diseases. In fact, four distinct types of protein accumulations found in age-related disorders can be placed on the list of therapeutic indications linked to the autophagy–lysosomal clearance pathway. Alzheimer's disease, Huntington's disease, tauopathies, and Parkinson's disease have the common feature of intracellular protein accumulation pathology (Alzheimer's disease also exhibits extracellular deposition). These proteinopathies are also similar in that they are generally characterized by the loss of neurons, synaptic integrity, and cognitive and/or motor ability. Protein species implicated in the diseases include: (1) pathological assembly states of Aβ_{42} peptide, (2) mutant huntingtin protein, (3) tau modifications that lead to paired helical filament (PHF) formation and neurofibrillary pathology of frontotemporal dementia and other tauopathies, and (4) point mutations in α-synuclein that enhance aggregation and cause dominant forms of Parkinson's disease. Interestingly, the four types of proteins are targeted by a common lysosomal clearance pathway involving the cysteine protease cathepsin B (CatB).

CatB was previously shown to degrade Aβ_{42} into smaller, less pathogenic peptides via carboxy-terminal truncation.[7] The study also found that genetic ablation of CatB, by crossing CatB$^{-/-}$ mice with human amyloid precursor protein (hAPP) transgenic mice, resulted in increased Aβ_{42} levels and the worsening of Aβ deposition and other Alzheimer-type pathologies. Correspondingly, Aβ deposition in mouse models of Alzheimer's disease was significantly reduced when CatB activity was enhanced by over-expressing the enzyme through lentiviral delivery[7] or by pharmacologically increasing the active form of CatB in neurons.[8,9] The latter utilized Z-phenylalanyl-alanyl-diazomethylketone (PADK), a cathepsin modulatory compound that selectively enhances CatB in lysosomes, resulting in decreased intracellular Aβ. The diminished Aβ_{42} levels in PADK-treated transgenic mice correlated with augmented measures of active CatB, increases in the truncated Aβ_{38} peptide, decreases in extracellular deposits, and reductions in cellular and behavioral disease parameters. Similar cathepsin modulation, Aβ clearance, and functional benefits resulted when endogenous inhibitors of lysosomal cysteine proteases were genetically deleted in mice expressing hAPP with familial Alzheimer's disease-linked mutations[10,11] or wild-type hAPP.[12]

The relationship between CatB and the Aβ peptide is similar to the relationship CatB has with other proteins of proteinopathies, including the link between mutant huntingtin protein and the lysosomal enzyme. Reducing CatB activity was found to worsen mutant huntingtin protein toxicity in primary neurons, whereas enhancing CatB activity led to autophagy-dependent neuroprotection.[13] In a related Huntington's disease study that specifically measured the clearance of a long-lived polyQ protein aggregate, induction of autophagy decreased the polyQ aggregates and, as in the other studies, this effect was abrogated by disrupting the activity of lysosomal enzymes.[14] In addition to Alzheimer's disease and Huntington's disease, the CatB relationship extends to the tau protein of tauopathies. Previous studies showed that CatB inhibition and lysosomal disruption cause an increase in both phosphorylated tau levels and intracellular PHF-tau aggregates in hippocampal tissue.[15,16] Correspondingly, reductions in phosphorylated 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

1. Bahr BA, Wisniewski ML, Butler D. Positive lysosomal modulation as a unique strategy to treat age-related protein accumulation diseases. Rejuvenation Res 2012;15:189–197.
2. Nixon RA. The role of autophagy in neurodegenerative disease. Nat Med 2013;19:983–997.
3. Rubinsztein DC, Codogno P, Levine B. Autophagy modulation as a potential therapeutic target for diverse diseases. Nat Rev Drug Discov 2012;11:709–730.
4. Eskelinen E-L, Saftig P. Autophagy: A lysosomal degradation pathway with a central role in health and disease. Biochim Biophys Acta (Mol Cell Research) 2009;1793: 664–673.
5. Lucin KM, Wyss-Coray T. Targeting autophagy for disease therapy. Nat Biotechnol 2013;31:322–323.
6. Shoji-Kawata S, Sumpter R, Leveno M, Campbell GR, Zou Z, Kinch L, Wilkins AD, Sun Q, Pallauf K, MacDuff D, Huerta C, Virgin HW, Helms JB, Eerland R, Tooze SA, Xavier R, Lenschow DJ, Yamamoto A, King D, Lichtarge O, Grishin NV, Spector SA, Kaloyanova DV, Levine B. Identification of a candidate therapeutic autophagy-inducing peptide. Nature 2013;494:201–206.
7. Mueller-Steiner S, Zhou Y, Arai H, Roberson ED, Sun B, Chen J, Wang X, Yu G, Esposito L, Mucke L, Gan L. Antiamyloidogenic and neuroprotective functions of cathepsin B: Implications for Alzheimer's disease. Neuron 2006;51:703–714.
8. Butler D, Hwang J, Estick C, Nishiyama A, Kumar SS, Baveghems C, Young-Oxendine HB, Wisniewski ML, Charalambides A, Bahr BA. Protective effects of positive lysosomal modulation in Alzheimer's disease transgenic mouse models. PLoS One 2011;6:e20501.
9. Viswanathan K, Hoover DJ, Hwang J, Wisniewski ML, Ikonne US, Bahr BA, Wright DL. Nonpeptidic lysosomal modulators derived from Z-Phe-Ala-diazomethylketone for treating protein accumulation diseases. ACS Med Chem Lett 2012;3:920–924.
10. Sun B, Zhou Y, Halabisky B, Lo I, Cho SH, Mueller-Steiner S, Devidze N, Wang X, Grubb A, Gan L. Cystatin C–cathepsin B axis regulates amyloid β levels and associated neuronal deficits in an animal model of Alzheimer's disease. Neuron 2008;60:247–257.
11. Yang DS, Stavrides P, Mohan PS, Kaushik S, Kumar A, Ohno M, Schmidt SD, Wesson D, Bandyopadhyay U, Jiang Y, Pawlik M, Peterhoff CM, Yang AJ, Wilson DA, St George-Hyslop P, Westaway D, Mathews PM, Levy E, Cuervo AM, Nixon RA. Reversal of autophagy dysfunction in the TgCRND8 mouse model of Alzheimer's disease ameliorates amyloid pathologies and memory deficits. Brain 2011;134:258–277.
12. Wang C, Sun B, Zhou Y, Grubb A, Gan L. Cathepsin B degrades amyloid-β in mice expressing wild-type human amyloid precursor protein. J Biol Chem 2012;287:39834–39841.
13. Liang Q, Ouyang X, Schneider L, Zhang J. Reduction of mutant huntingtin accumulation and toxicity by lysosomal cathepsins D and B in neurons. Mol Neurodegener 2011; 6:37.
14. Ju JS, Miller SE, Jackson E, Cadwell K, Piwnica-Worms D, Weihl CC. Quantitation of selective autophagic protein aggregate degradation in vitro and in vivo using luciferase reporters. Autophagy 2009;5:511–519.
15. Bendiske J, Caba E, Brown QB, Bahr BA. Intracellular deposition, microtubule destabilization, and transport failure: An ''early'' pathogenic cascade leading to synaptic decline. J Neuropathol Exp Neurol 2002;61:640–650.
16. Ryzhikov S, Bahr BA. Gephyrin alterations due to protein accumulation stress are reduced by the lysosomal modulator Z-Phe-Ala-diazomethylketone. J Mol Neuroscience 2008;34:131–139.
17. Bendiske J, Bahr BA. Lysosomal activation is a compensatory response against protein accumulation and synaptopathogenesis—an approach for slowing Alzheimer's disease? J Neuropathol Exp Neurol 2003;62:451–463.
18. Lee HJ, Khoshaghideh F, Patel S, Lee SJ. Clearance of α-synuclein oligomeric intermediates via the lysosomal degradation pathway. J Neurosci 2004;24:1888–1896.
19. Boassa D, Berlanga ML, Yang MA, Terada M, Hu J, Bushong EA, Hwang M, Masliah E, George JM, Ellisman MH. Mapping the subcellular distribution of α-synuclein in neurons using genetically encoded probes for correlated light and electron microscopy: Implications for Parkinson's disease pathogenesis. J Neurosci 2013;33:2605–2615.
20. Savolainen MH, Richie CT, Harvey BK, Männistö PT, Maguire-Zeiss KA, Myöhänen TT. The beneficial effect of a prolyl oligopeptidase inhibitor, KYP-2047, on α-synuclein clearance and autophagy in A30P transgenic mouse. Neurobiol Dis 2014;68:1–15.

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