

*Viewpoint*

## Organelle-Specific Autophagy in Cellular Aging and Rejuvenation

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### ABSTRACT

The health of a cell requires proper functioning, regulation, and quality control of its organelles, the membrane-enclosed compartments inside the cell that carry out its essential biochemical tasks. Aging commonly perturbs organelle homeostasis, causing problems to cellular health that can spur the initiation and progression of degenerative diseases and related pathologies. Here, we discuss emerging evidence indicating that age-related defects in organelle homeostasis stem in part from dysfunction of the autophagy-lysosome system, a pivotal player in cellular quality control and damage clearance. We also highlight natural examples from biology where enhanced activity of the autophagy-lysosome system might be harnessed to erase age-related organelle damage, raising potential implications for cellular rejuvenation.

**KEYWORDS:** cell biology; autophagy; organelles; aging; rejuvenation

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### Open Access

Received: 30 December 2020

Accepted: 06 April 2021

Published: 09 April 2021

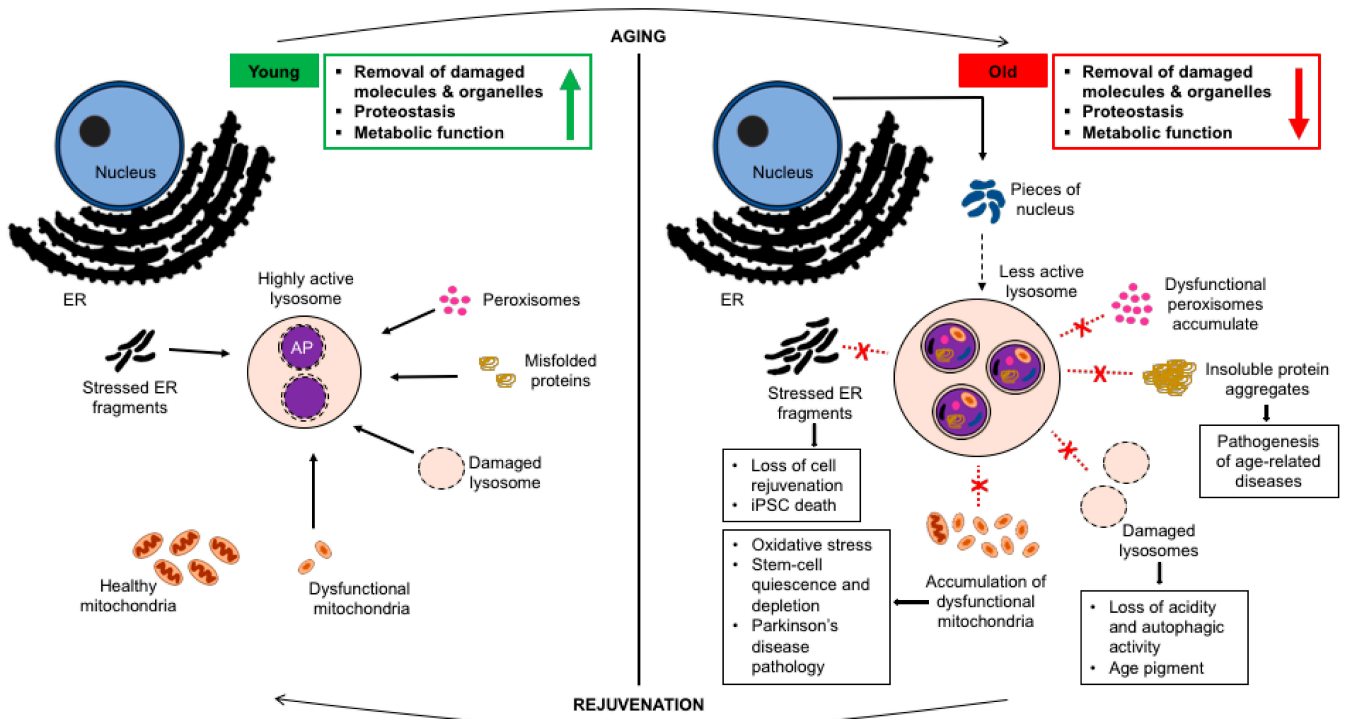
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In eukaryotic cells, molecular waste and damaged materials can be delivered to lysosomes for enzymatic degradation via autophagy [1]. During this process, autophagic vesicles, termed autophagosomes, form around select cargo, then subsequently fuse with the lysosome to allow for targeted degradation. Though autophagosomes were first observed by electron microscopy in the mid-1950s [2], it was not until nearly 40 years later that the first autophagy genes were identified in yeast [3–5]. Since then, breakthroughs in live-cell imaging have enabled sophisticated, real-time imaging of the autophagic process in several eukaryotic species, including animals [6,7]. In addition, an expanding pharmacological toolkit of molecules that modify autophagic activity in vivo (Table 1) has facilitated manipulation of this system in live organisms and raised exciting therapeutic prospects.

A defining feature of the autophagy-lysosome system is its unique ability to recalibrate cellular homeostasis in response to a cell's needs. If a cell is under intrinsic or extrinsic stress, activation of autophagy can help to erase molecular damage and to recycle material needed to support basic biological

functions [1]. When these mechanisms fail, the stress can amplify, leading to an irreparable collapse in cellular homeostasis. Notably, aging is accompanied by several molecular signs of stress. As cells get older, genetic instability increases, proteins cluster into non-functional aggregates, and organelles, the cellular mini-factories that execute distinct signaling and metabolic functions, become damaged and inefficient [8]. Is this age-related collapse in cellular health and homeostasis linked to defects in autophagy?

Remarkably, researchers have found that an early-age decrease in lysosome and autophagic activity may be an initiating “domino” in age-related cellular deterioration [9,10]. Consistent with this model, modifying autophagic activity has profound effects on the aging process; experimental inhibition of lysosomal and/or autophagic factors accelerates aging in various organisms [11–14], whereas interventions that boost autophagic activity delay the appearance of cellular signs of aging and extend lifespan [15–17]. Even human centenarians [18], like long-lived mutant animals [19], have been reported to display exceptionally high levels of autophagic activity. These and other findings highlight the autophagy-lysosome system as an emerging nexus in the control of aging and longevity (Figure 1). Still, molecular details of this regulation remain obscure.



**Figure 1. Changes to autophagy of cellular organelles during the aging process.** Lysosomes in young, healthy cells (on the left) are acidic and effectively degrade cellular waste, including organelles when necessary. This maintains robust homeostasis, which supports proper functioning not only of a cell but of a whole organism. However, in an old cell (on the right), lysosome dysfunction jeopardizes autophagic turnover, causing a build-up of damaged organelles along with protein aggregates; this leads to several age-related disease pathologies and brings about changes to organismal physiology. Re-establishing the correct dynamics of organelle turnover at lysosomes in old cells might provide one entry point to trigger a rejuvenation of cellular health and homeostasis. AP, autophagosome.

For one, how is different autophagic cargo handled in aging cells, and do changes to cargo turnover directly contribute to the aging process? Many studies have investigated how defective autophagy impedes protein-aggregate clearance in old cells [20]. This is an important line of research, given that impaired protein homeostasis ('proteostasis') is characteristic of many age-related diseases, including Alzheimer's [21]. Yet, defective organelles are also common to age-related diseases [22–24], and their turnover is likewise sensitive to lysosome dysfunction [1,25]. To date, surprisingly little is known about the dynamics and control of organelle turnover in aging cells. Clarifying the regulation of organelle-specific autophagy during aging could provide novel clues on the biological basis of age-related disease, and might also hint at therapies for fighting the aging process.

Perhaps the most information is currently known regarding the age-related regulation of mitochondria, the energetic hubs of a cell. With age, mitochondrial function and homeostasis break down. Several proteins involved in oxidative phosphorylation and fatty-acid metabolism, two key cellular processes that occur at mitochondria, have been reported to decrease in abundance in old animals [26–28]. These molecular alterations, combined with other age-induced changes to mitochondrial protein levels and stoichiometry [29], are thought to impair mitochondrial activity and destabilize cellular bioenergetics and metabolism. As a consequence of this dysfunction, fragmented, oxidatively-damaged mitochondria are commonly seen in old cells of diverse eukaryotic species, ranging from yeasts to mammals [8,9,30–32]. Though healthy cells can effectively eliminate dysfunctional mitochondrial fragments by mitochondrial autophagy, or 'mitophagy' [33], mitochondrial-clearance mechanisms show signs of failure in old age [34,35]. This disrupts the balance between mitochondrial biogenesis and degradation, causing an age-dependent increase in damaged mitochondria that further exacerbates cell stress [34]. Mitophagy defects can predispose humans to degenerative disease; indeed, dysfunction of mitophagy factors, including Parkin and PINK1, is commonly seen in Parkinson's disease patients [36,37]. Thus, impaired turnover of damaged organelles is at least partly to blame for some of the classic aging pathologies commonly seen in the clinic.

Importantly, impaired turnover with age does not appear to be limited to mitochondria. In cells, lysosomes are responsible for degrading additional types of organelles, including portions of the endoplasmic reticulum (ER), peroxisomes, and even other lysosomes. Like mitochondrial damage, ER stress accumulates in old cells [38]. Strikingly, genetic inhibition of ER-phagy causes progeric phenotypes and shortened lifespan in mice [39], hinting that ER turnover might be required to slow the pace of aging. Additionally, peroxisomes and lysosomes have been reported to increase in abundance in late age in some species and cell types [40,41]. In fact, uncleared lysosomes generate a non-degradable, autofluorescent 'age pigment', which has been used as a visual readout for

biological age in multiple systems [42–44]. It will be important to clarify how directly these age-related changes in organelle number reflect impairment of the autophagy-lysosome system, and whether these changes bring about physiological effects on metabolic functioning in old animals.

While the general trend is that organelle turnover appears to decline with advanced age due to autophagy-lysosome dysfunction (Figure 1), this may not be true of all organelles, or for all stages of the aging process. For example, pieces of the nucleus are degraded at lysosomes in aging worms, even in the healthiest of individuals [45]. How nuclear autophagy ('nucleophagy') regulates organismal physiology, particularly during aging, is unclear, but it may be protective, as suggested in mouse models of laminopathies [46]. It remains to be seen whether other organelles likewise undergo regulated, active turnover in aging animals. Some organelles may even be degraded in early aging but start to accumulate later once lysosomes become dysfunctional. Understanding the dynamics and timing of organelle turnover at different stages of aging could reveal complexities that affect aging rate and/or stochasticity among different individuals in a population.

If organelle damage is generally characteristic of very old age, could harnessing organelle-specific autophagy help an old cell to regain its vitality and youthfulness? Germ (reproductive) cells provide a unique opportunity to study cellular rejuvenation, because age is naturally reset across generations. We and others have shown that cellular damage, including defective mitochondria, can be rapidly reversed as oocytes prepare for fertilization [47,48]. Removal of dysfunctional molecules and organelles is also seen during gametogenesis in single-celled yeast [49]. These findings imply that damage-clearance mechanisms may function centrally to the biological mechanisms of transgenerational rejuvenation. In support of this interpretation, lysosomes are activated in maturing oocytes prior to fertilization [47], and, once active, they could conceivably clear various forms of cellular damage, including dysfunctional organelles, to reset cellular health and homeostasis across generations. Though the specific cargo received by oocyte lysosomes awaits full description, identification of natural mechanisms that renew organelle health in the immortal germ-cell lineage could point the way to new strategies to counteract organelle damage in old somatic cells.

Lysosome induction has been reported to also occur during stem-cell activation and differentiation [50–52]. In these contexts, as in oocyte maturation, lysosome activation is linked to a developmental rewiring of cellular metabolism. Though, again, much attention has been paid to the role of lysosome activity in stem-cell proteostasis, there is recent evidence that organelle-specific autophagy plays a fundamental role in stem-cell and regenerative biology [53–57]. For one, impaired mitophagy leads to muscle stem-cell quiescence in old mice, and re-establishing autophagic flux is sufficient for old muscle stem cells to exit quiescence and regain

stemness [58]. Importantly, defective mitophagy appears to cause oxidative stress and stem-cell depletion in other cell types as well [59,60]. These findings hint that mitochondrial turnover might be a pivotal determinant of regenerative capacity.

Notably, mitophagy also appears important in the generation of induced pluripotent stem cells (iPSCs) [57,61]. A number of rejuvenating events, including telomere re-lengthening and organelle renewal, have been associated with iPSC generation from differentiated cells [62–64]. Inhibiting mitochondrial fission, one of the early steps in mitophagy induction [33,65], prevents the conversion of fibroblasts to iPSCs [61]. Thus, it is exciting to speculate that organelle-specific autophagy may be integrated with other rejuvenating events involved in iPSC reprogramming, and that enhancing these activities might provide an entry point to improve the efficiency of this process.

Beyond mitophagy, other forms of organelle-specific autophagy are only beginning to be studied in the context of cellular regeneration and rejuvenation. Interestingly, elevated ER stress has been linked to iPSC death [66], and significant ER remodeling occurs as part of iPSC reprogramming [67]. In principle, ER quality control mechanisms, including ER-phagy, could aid regenerative capacity, particularly in old animals where persistent ER stress abounds [38]. As a compelling corollary, the ER has been shown to undergo dramatic rearrangements coincident with oocyte maturation and lysosome activation in the *C. elegans* germline [68]. How the ER and lysosomes are functionally and/or mechanically linked to support cellular rejuvenation is an important open question moving forward, as is the involvement of other organelle-turnover events in cellular-rejuvenation mechanisms.

In summary, dynamic changes to the landscape of the cell occur during aging, and several of these age-related changes can be traced to alterations in organelle homeostasis and turnover (Figure 1). Harnessing the natural rejuvenating capacities of the autophagy-lysosome system provides one possible means to reverse age-related organelle damage and re-establish a more youthful cellular environment (Figure 1). In fact, pharmacological tools that boost lysosome function (Table 1) are currently being tested as potential anti-aging therapies in old animals and humans [69,70]. Looking forward, it seems likely that growing knowledge on the mechanistic principles that govern organelle turnover at lysosomes, and the specific parts of these systems that fail with old age, will open new doors for aging-biology researchers in the quest to promote healthy aging, particularly at a cellular level.

**Table 1.** Example drugs that modulate autophagy in vivo.

<b>Drug</b>	<b>Mode of action</b>	<b>Reference</b>
<i>Inducers</i>		
Rapamycin	Inhibits mTOR pathway	[15,71–73]
Torin1	Inhibits mTOR pathway	[74,75]
PP242	Inhibits mTOR pathway	[76]
Curcumin	Activates Transcription factor EB; Inhibits mTOR pathway; Activates ERK1/2 pathway	[77,78]
Metformin	Activates Sirtuin-1	[79]
Resveratrol	Activates Sirtuin-1	[80]
Trehalose	Inhibits SLC2a family of glucose transporters; Activates AMPK	[81]
Spermidine	Regulates acetylation and deacetylation of cellular proteins	[82,83]
Lithium	Reduces inositol triphosphate levels	[84,85]
Carbamazepine	Reduces inositol triphosphate levels	[86,87]
Valproic acid	Reduces inositol triphosphate levels	[88]
<i>Inhibitors</i>		
Chloroquine	Impairs lysosomal acidification	[10,73,89]
Lys05	Impairs lysosomal acidification	[90]
Wortmannin	Inhibits phosphatidylinositol 3-kinases	[91]
Bafilomycin A1	Inhibits V-ATPase; Inhibits autophagosome-lysosome fusion	[19,92,93]
Spautin-1	Inhibits USP10 and USP13, which regulate deubiquitination of Beclin-1	[94,95]
DBeQ	Inhibits p97/VCP	[96]

### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

### FUNDING

We acknowledge funding from the LSU Office of Research and Economic Development, the LSU College of Science, and the LSU Department of Biological Sciences, as well as grants from the National Institutes of Health (R03AG067125; KAB) and the W. M. Keck Foundation (KAB). KAB is also a Glenn Foundation for Medical Research and AFAR Grant for Junior Faculty awardee.

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How to cite this article:

Butsch TJ, Ghosh B, Bohnert KA. Organelle-Specific Autophagy in Cellular Aging and Rejuvenation. *Adv Geriatr Med Res*. 2021;3(2):e210010. <https://doi.org/10.20900/agmr20210010>