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Review

The crucial impact of lysosomes in aging and longevity

Didac Carmona-Gutierrez[a,1], Adam L. Hughes[b,1], Frank Madeo[a,c], Christoph Ruckenstuhl[a,*]

[a] Institute of Molecular Biosciences, NAWI Graz, University of Graz, 8010 Graz, Austria
[b] University of Utah, Department of Biochemistry, Salt Lake City, UT 84112-5650, USA
[c] BioTechMed, Graz, Austria

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ABSTRACT

Lysosomes are the main catabolic organelles of a cell and play a pivotal role in a plethora of cellular processes, including responses to nutrient availability and composition, stress resistance, programmed cell death, plasma membrane repair, development, and cell differentiation. In line with this pleiotropic importance for cellular and organismal life and death, lysosomal dysfunction is associated with many age-related pathologies like Parkinson's and Alzheimer's disease, as well as with a decline in lifespan. Conversely, targeting lysosomal functional capacity is emerging as a means to promote longevity. Here, we analyze the current knowledge on the prominent influence of lysosomes on aging-related processes, such as their executory and regulatory roles during general and selective macroautophagy, or their storage capacity for amino acids and ions. In addition, we review and discuss the roles of lysosomes as active players in the mechanisms underlying known lifespan-extending interventions like, for example, spermidine or rapamycin administration. In conclusion, this review aims at critically examining the nature and pliability of the different layers, in which lysosomes are involved as a control hub for aging and longevity.

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1. Introduction

Lysosomes are found in all animal cell types (except erythrocytes) and represent the cell's main catabolic organelles. The variety of substrates degraded in the lysosomes is wide, ranging from intracellular macromolecules and organelles to surface receptors and pathogens, among others. To exert their catabolic function, lysosomes contain an extensive set of hydrolases, including proteases,

* Corresponding author.
E-mail address: ru.ruckenstuhl@uni-graz.at (C. Ruckenstuhl).
[1] These authors contributed equally.

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nucleases, lipases, sulfatases or phosphatases, whose pH optima are usually low (pH 4.5–5). Accordingly, their degradative capacity depends on a highly acidic milieu, which is maintained via the activity of a proton-pumping V-type ATPase that pumps protons from the cytoplasm into the lysosomal lumen. However, lysosomes are not mere sites for disposal and processing of cellular waste but also act as pivotal regulators of cell homeostasis at different levels. For instance, they are involved in the regulation of cellular responses to nutrient availability and composition, stress resistance, programmed cell death, plasma membrane repair, development, and cell differentiation, among many others (Braun et al., 2015a,b; Boya, 2012; Settembre et al., 2013b). Thus, lysosomes play a determining role in processes that control cellular and organismal life and death.

Concurring with this pleiotropic importance, lysosomal dysfunction is associated to a plethora of disorders. Among them are those collectively known as lysosomal storage diseases (LSDs), which involve approximately 50 individual rare pathologies, whose combined incidence, however, is estimated to be about 1:5000 live births (Fuller et al., 2006; Platt et al., 2012). LSDs are characterized by an anomalous accumulation of undigested intra-lysosomal material and each disease is caused by a specific monogenic deficiency, respectively. Mutations most commonly affect acidic hydrolases, but can also be found in non-enzymatic lysosomal proteins (soluble and membrane-bound) and non-lysosomal factors regulating lysosomal function. LSDs typically manifest in neurodegeneration during infancy/childhood and in some milder variants during adulthood (Nixon et al., 2008; Wraith, 2002). Accordingly, though tissue degeneration occurs in different organs (Beltroy et al., 2005), LSD progression most markedly triggers neuronal loss in patients and mouse models (Sleat et al., 2004; Tessitore et al., 2004; Walkley and Suzuki, 2004). In fact, the nervous system seems to be particularly susceptible to defects in lysosomal function (Hara et al., 2006; Komatsu et al., 2006). In addition to LSDs, age-related neurodegenerative disorders like Alzheimer's or Parkinson's disease are connected to impaired lysosomal activity through different but interweaved mechanisms that seem to include lysosomal enzyme malfunction, reduced intraluminal acidification or disrupted calcium regulation (Büttner et al., 2013; Jiang and Mizushima, 2014; McBrayer and Nixon, 2013; Menezes et al., 2015; Wolfe et al., 2013). For instance, mutations in glucocerebrosidase (GBA), a lysosomal glucosylceramidase, are associated to an increase in the risk for Parkinson's Disease (Westbroek et al., 2011). Reduced GBA activity has thereby been linked to increased levels of alpha-synuclein, a small protein, whose abnormal accumulation as aggregates is characteristic of synucleopathies like Parkinson's Disease (Westbroek et al., 2011). Notably, lysosomal defects disturb the balance between damaged proteins and their proteolytic clearance, ultimately resulting in the accumulation of highly cross-linked aggregates. Accumulation of aggregates in post-mitotic cells appears to be particularly dramatic, since the material cannot be diluted via cell division. Many resulting aggregates of oxidized proteins may further react with cellular components like lipids and metals in different compositions, forming a fluorescent material termed lipofuscin (Jung et al., 2007). The exact cellular effects of lipofuscin are largely hypothetical and still under discussion, but may e.g. involve the production of oxidants, possibly via iron-mediated catalysis of free radicals (Höhn et al., 2010), or the inhibition of the proteasome (Höhn et al., 2011).

Of note, all the mentioned diseases exhibit a decline in healthspan and/or lifespan. Indeed, the aging process itself may be fueled by a decrease in lysosomal function. This may occur at several molecular levels, according to the multiple functions of the lysosomes and their broad intracellular impact. For instance, lysosomal degradation is tightly connected to the process of autophagy, the intracellular self-digestion machinery that orchestrates the elimination of unwanted or damaged material (e.g. macromolecules, organelles) that accumulates during aging (Klionsky, 2007; Madeo et al., 2015; Nakamura et al., 1997; Pierce et al., 2007; Sampaio-Marques et al., 2014). Thereby, lysosomes are not only the terminal degradation compartments, but are also connected to the autophagic process at the signaling level. For example, they represent a molecular hub controlling the activity of the mammalian target of rapamycin complex 1 (mTORC1) kinase complex, a negative master regulator of autophagy. Also, they are linked to the transcription factor EB (TFEB), which regulates both lysosomal biogenesis and autophagy activation (Settembre et al., 2013b). Besides their central implication in autophagy, lysosomes seem to crucially contribute to lifespan control via a diverse array of other signals as shown in different model organisms. For instance, deployment of active lipid molecules from the lysosomes to the nucleus results in altered gene expression that modulates lifespan in worms (Folick et al., 2015). Another aging-relevant signal might be the intralysosomal pH (Hughes and Gottschling, 2012), which impacts the degradative and storage functions of the lysosome in yeast. In fact, stored amino acids and metals like iron and calcium can significantly influence aging at several levels (Hughes and Gottschling, 2012; Klang et al., 2014; Kurz et al., 2007; Medina et al., 2015; Smaili et al., 2013). In this review, we will analyze the current evidence for these and other lysosome-lifespan connections and discuss the participation and pliability of lysosomal function in the frame of known anti-aging interventions (Fig. 1).

2. Lysosomes and the regulation of autophagy during aging

An organism's survival depends on its ability to maintain a balance between the production of new and the degradation of old and potentially harmful proteins and cellular structures. This balance is strongly dictated by the catabolic capacity of a cell, which is mainly executed via two distinct processes. On the one hand, the ubiquitin/proteasomal degradation pathway, which functions at the cytosolic level, primarily targets cytosolic proteins, ER proteins following their retrograde transport to the cytosol, and ubiquitinated mitochondrial proteins exposed on the outer membrane of mitochondria (Finley, 2009; Glickman and Ciechanover, 2002; Walter and Ron, 2011). On the other hand, the autophagic machinery degrades a wide array of cytosolic substrates, ranging from single proteins to whole organelles that are delivered to the lysosome for hydrolytic dismantling. Both degradation pathways have been associated to aging control (Carrard et al., 2002; Chondrogianni and Gonos, 2005; Cuervo and Dice, 2000; Kurz et al., 2008; Löw, 2011; Terman et al., 2010). Interestingly, they also seem to interact with each other (Ciechanover, 2005; Korolchuk et al., 2010), even though the regulatory extent of this crosstalk in the frame of lifespan control needs further investigation.

2.1. Lysosomal execution during autophagy

Autophagy can mainly be divided into three subroutines: chaperone-mediated autophagy (CMA), microautophagy and macroautophagy (Singh and Cuervo, 2011). While all of them directly depend on functional lysosomes, the underlying mechanisms are distinct. During CMA, the cytosolic heat shock cognate 70 (hsc70) chaperone and its co-chaperones recognize the consensus motif (KFERQ) in target cytosolic proteins and are transported to the lysosomal membrane. There, lysosome-associated protein type 2A (LAMP-2A) is recognized by this substrate chaperone complex, allowing the target protein to unfold and cross the lysosomal membrane. CMA is thus characterized by selective protein targeting and direct substrate translocation to the lysosomes, which establishes a singular role of this process in diverse pathophysiological conditions, including aging (Cuervo, 2011; Dice, 2007; Martinez-Lopez

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