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Review

Lysosomes: Signaling Hubs for Metabolic Sensing and Longevity

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Lysosomes are sites of active metabolism in a cell. They contain various hydrolases that degrade extracellular and intracellular materials during endocytosis and autophagy, respectively. In addition to their long-recognized roles in degradation and recycling, emerging studies have revealed that lysosomes are organizing centers for signal transduction. Lysosome-derived signaling plays crucial roles in regulating nutrient sensing, metabolic adaptation, organelle crosstalk, and aging. In particular, how the degradative role of the lysosome cooperates with its signaling functions to actively modulate lifespan is beginning to be unraveled. This review describes recent advances in the role of the lysosome as a 'signaling hub' that uses three different lysosome-derived signaling pathways to integrate metabolic inputs, organelle interactions, and the control of longevity.

Highlights

The lysosome serves as a signaling center to integrate extracellular and intracellular inputs, and accordingly regulates cellular homeostasis and organism fitness.

mTORC1 at the lysosomal surface responds to amino acid and cholesterol signals from the lysosomal lumen, and coordinates downstream pathways involved in aging control.

AMPK is recruited to the lysosomal surface for activation in response to glycolytic signals, and promotes longevity via specific downstream effectors.

Specific lipid messengers and chaperones mediate lysosome-to-nucleus retrograde signaling communication to improve interorganelle crosstalk, redox homeostasis, and longevity.

Introduction

The discovery of the intracellular organelle, the lysosome, dates back to the early 1950s when Nobel laureate Christian de Duve characterized the glucose-6-phosphatase-mediated mechanism using tissue-fractionation techniques and identified exclusive 'lytic bodies', ultimately named lysosomes [1,2]. These cytoplasmic granules constitute an acidic environment (pH ranging between 4.5 and 5.5) and carry ~60 types of hydrolytic enzymes, including lipases, proteases, glucosidase, acid phosphatases, nucleases, and sulfatases, making lysosomes the main cellular compartment for breaking down and recycling diverse macromolecules [3–5]. The luminal hydrolases are enclosed by a single phospholipid bilayer membrane which contains integral transmembrane proteins, including the vacuolar-type H^+-ATPase (v-ATPase) that pumps protons from the cytoplasm into the lysosomal lumen to maintain an acidic pH [6,7], ion channels that establish lysosomal membrane potential, and permeases and transporters that facilitate the release of end-products from lysosomal hydrolysis [8–10].

Through receiving and degrading macromolecules from secretory, endocytic, autophagic, and phagocytic trafficking pathways, lysosomes are able to integrate both extracellular and intracellular inputs, and regulate diverse cellular processes such as pathogen defense, metabolic adaptation, and organelle crosstalk [11–14]. Recent discoveries also reveal that lysosomes regulate signal transduction and nuclear transcription to govern cell and organism homeostasis. In particular, both lysosome-mediated metabolic and signaling processes contribute to longevity regulation. One of these regulatory mechanisms is linked to autophagy, a self-digestive process that requires lysosomal function for degradation and recycling, and the involvement of autophagy in multiple prolongevity paradigms has been summarized in several reviews [15–19]. We focus here on the emerging role of the lysosome as a 'signaling hub' that integrates metabolic inputs, directs organelle crosstalk, and governs the regulation of longevity (Figure 1, Key Figure), with emphasis on lysosome-to-nucleus retrograde signaling pathways mediated by mTORC1, AMP-activated protein kinase (AMPK), and lipid metabolism.

Lysosomal Amino acid Signaling through the mTORC1–TFEB/TFE3 Axis

Mechanistic/mammalian target of rapamycin complex 1 (mTORC1), one of two distinct protein complexes that use the serine/threonine kinase mTOR as a catalytic subunit, is a major regulator of cell growth and metabolism [20–23]. Various inputs from amino acids, growth factors, hormones, and stress can converge on mTORC1 to activate diverse downstream signaling mechanisms responsible for different cellular responses [23–25]. Studies in yeast to mice have demonstrated that inhibition of mTOR signaling either genetically or pharmacologically can extend lifespan, and have placed autophagy as the master downstream effector of the mTOR-mediated longevity pathway [26–32]. Recent findings have also shown a direct link between lysosomes and mTOR signaling, which is necessary for coordinating amino acid sensing and mTORC1 activation (Figure 2) [33]. Indeed, lysosomes carry a

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Key Figure

Lysosomal Signaling Pathways in Longevity Regulation.

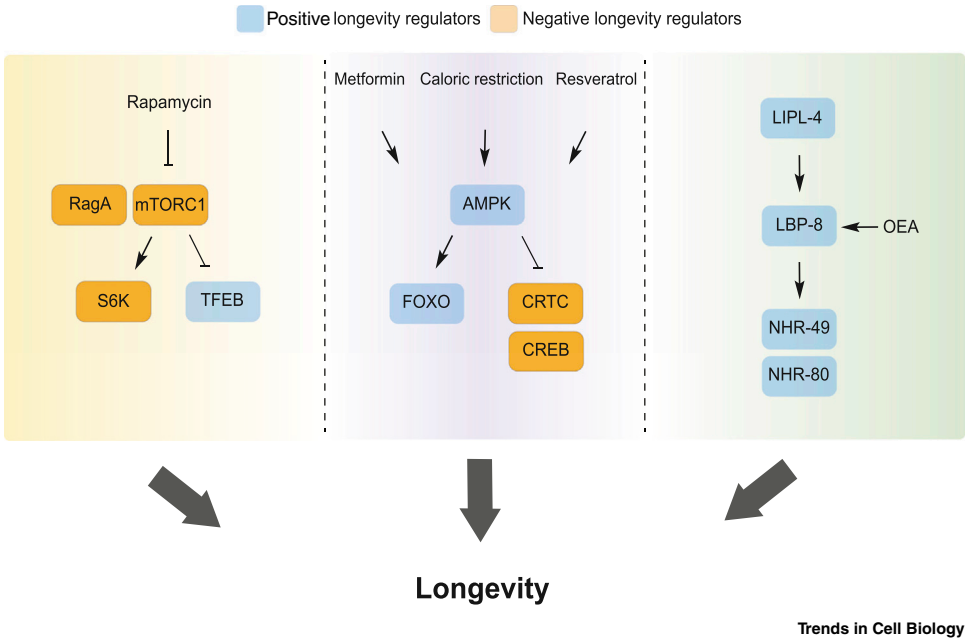

Figure 1. Genetic or pharmacological modification of three lysosomal signaling pathways promotes longevity. Positive regulators labeled in blue are genes whose induction extends lifespan, and negative regulators labeled in orange are genes whose inhibition extends lifespan. LIPL-4, LBP-8, NHR-49, and NHR-80 use *Caenorhabditis elegans* nomenclature, and the others are based on mammalian nomenclature. Abbreviation: OEA, oleoylethanolamide.

series of proteases that are responsible for the degradation of proteins into amino acids, and can function as a reservoir that preferentially stores basic amino acids such as arginine [34]. These findings inspire a new way of thinking not only about the mTOR regulatory mechanism but also about lysosome-derived signaling in the control of aging and longevity.

As a megadalton protein kinase complex, mTORC1 comprises three core components, mTOR, Raptor, and mLST8 [20,22,35]. Amino acid availability stimulates mTORC1 activity by signaling through the Rag family of small GTPases that recruit mTORC1 to the lysosomal surface [36–38]. Rag GTPases exist as heterodimers consisting of RagA or RagB in complex with RagC or RagD. The function of Rag GTPases depends on their nucleotide loading state, which is regulated by both guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs), including Ragulator (a GEF for RagC), GATOR1 (a GAP for RagA/B), and FLCN in complex with FNIP (a GAP for RagC/D) [37–43]. In particular, Ragulator consists of five LAMTOR subunits, and LAMTOR1 links LAMTOR2/3 and LAMTOR4/5 heterodimers together and anchors the whole complex to the lysosomal surface via its palmitoyl and myristoyl N-terminal groups [44]. The Rag GTPase heterodimer is tethered to the lysosome by this pentameric Ragulator complex, and, in response to amino acid signals, its nucleotide loading state changes from RagA/B^{GDP}–RagC/D^{GTP} to RagA/B^{GTP}–RagC/D^{GDP}, resulting in binding of Raptor and translocation of mTORC1 to the lysosomal surface [37]. This lysosomal translocation enables the interaction with Rheb, a small GTPase located at the lysosomal surface, which is required for mTORC1 kinase activity toward downstream effectors [45,46]. Being a small

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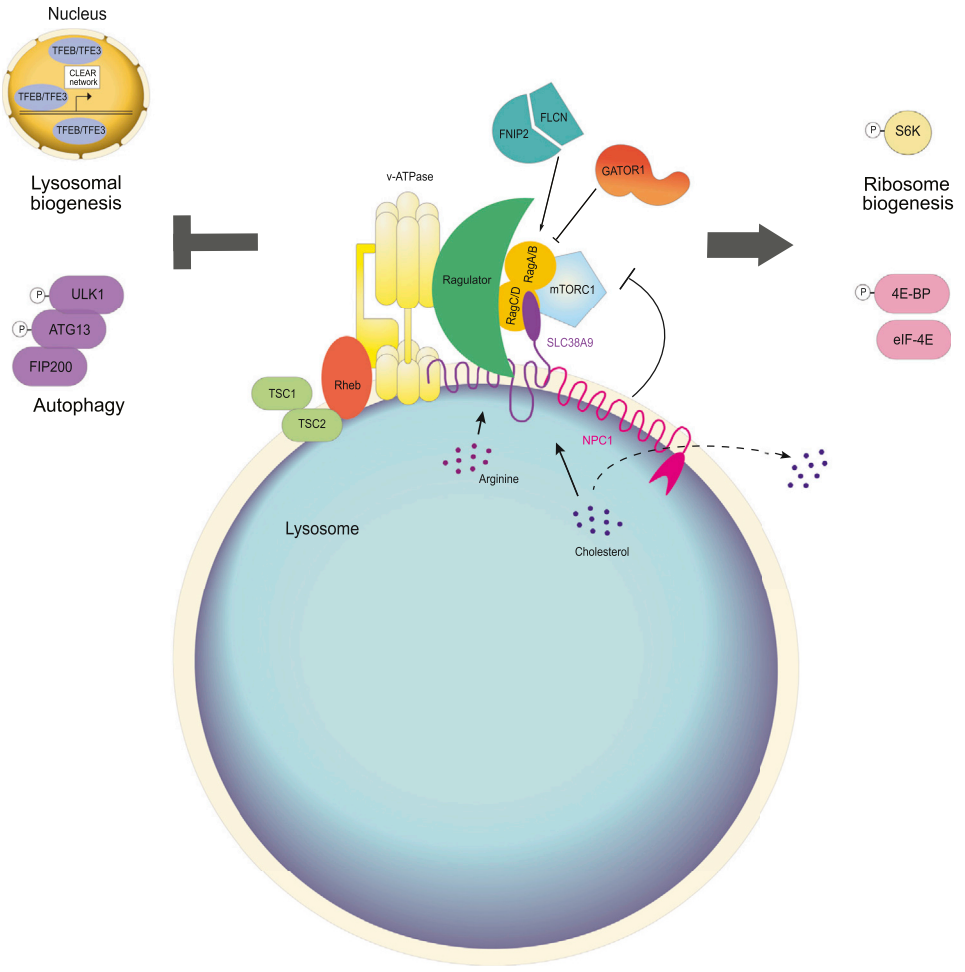

Figure 2. Lysosomal Lumen Amino Acid Sensing by mTORC1.
Specific amino acids (e.g., arginine) within the lysosomal lumen directly bind to SLC38A9 and signal through the v-ATPase–Ragulator complex to promote the GTP-binding state of RagA/B. Moreover, cytosolic amino acids activate the FLCN–FNIP complex, resulting in GTP hydrolysis in RagC/D. The Rag GTPase heterodimer in the state of RagA/B^{GTP}–RagC/D^{GDP} recruits mTORC1 to the lysosome surface where Rheb resides. Rheb stimulates mTORC1 activity toward downstream substrates. The TSC complex localized at the lysosomal surface functions as a GTPase-activating protein (GAP) of Rheb to negatively regulate mTORC1. Activated mTORC1 phosphorylates (P) multiple downstream substrates, and several examples are listed.

GTPase, the Rheb nucleotide loading state can be regulated by its GAP, the tuberous sclerosis complex (TSC), that is also localized on the lysosomal surface [47–49].

Although mTORC1 is a known sensor of amino acids in the cytoplasm [50–53], the lysosomal localization of mTORC1 raises a possibility that specific sensor proteins may relay inputs from lysosomal luminal amino acid pools to mTORC1. In searching for such proteins, v-ATPase has been shown to be involved in detecting lysosomal amino acid availability and consequently in mediating the activation of mTORC1 [33,54]. A small molecule that covalently modifies a unique cysteine of v-ATPase can specifically inhibit the lysosomal activation of mTORC1 [55]. The discovery of SLC38A9, a lysosomal arginine transporter in the Ragulator–Rag complex, further supports this lysosomal amino acid sensing model [51,56,57]. SLC38A9 interacts with Rag GTPase and Ragulator on the cytoplasmic

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side, and with v-ATPase via the transmembrane region. SLC38A9 also exhibits low affinity for polar amino acids, especially arginine [51,57]. By sensing lysosomal arginine levels, the activation of SLC38A9 converts the nucleotide loading state of RagA and stimulates mTORC1 activity [42]. In this way, the amino acid status of the lysosome signals through mTORC1 to actively regulate cellular activity.

Activated mTORC1 can phosphorylate different downstream protein substrates to coordinate the balance between biosynthesis and catabolism. For example, phosphorylation of p70S6 kinase (S6K) by mTORC1 promotes mRNA translation initiation and elongation [58–60], phosphorylation of eIF4E binding protein (4EBP) triggers 5′ cap-dependent mRNA translation [61,62], and phosphorylation of ULK1–ATG13–FIP2000 kinase complex inhibits autophagosome biogenesis [63–66]. Importantly, mTORC1 also regulates lysosomal gene expression by controlling the cytoplasmic–nuclear shuttling of transcription factors TFEB and TFE3 [67–70]. Both TFEB and TFE3 belong to the microphthalmia-associated transcription factor subfamily of basic helix-loop-helix transcription factors [71], and specifically bind to the CLEAR (coordinated lysosomal expression and regulation) motif to drive the transcription of genes involved in lysosomal biogenesis and autophagic machinery [68,72]. Activated mTORC1 at the lysosomal surface can phosphorylate TFEB at serines 142 and 211, and TFE3 at serine 321, respectively, and trigger their interaction with 14-3-3 protein, resulting in the cytoplasmic retention of these transcription factors [67,69,73]. Conversely, inhibition of lysosomal function reduces mTORC1-dependent phosphorylation of TFEB/TFE3 and promotes their nuclear translocation to induce lysosomal biogenesis and autophagy pathways [67–70]. Animal studies also reveal the crucial role that TFEB and TFE3 play in lipid metabolism and energy homeostasis through regulating metabolic gene expression [74–77].

These studies demonstrate that mTOR is a crucial lysosomal signal that couples the metabolic status of the lysosome with translational and transcriptional controls, and reveal that TFEB/TFE3 is a key messenger between the lysosome and the nucleus that executes metabolic regulation. Importantly, as a master regulator of cellular growth and metabolism, mTOR–TFEB/TFE3 signaling plays a key role in the control of aging and longevity (Figure 1). Genetic reduction of mTOR or S6K extends lifespan in yeast, worms, fruit flies, and mice [30,32,78–83]. Pharmaceutical inhibition of mTOR by rapamycin exerts similar prolongevity effects on diverse organisms from yeast to mice [26–29,31]. Furthermore, as a specific lysosomal mediator of mTORC1 activation, Rag GTPases have also been linked to longevity regulation, and their reduction extends lifespan in *Caenorhabditis elegans* [31,84]. Conversely, overexpression of HLH-30, the *C. elegans* homolog of TFEB/TFE3, promotes longevity [85]. In mouse models of Alzheimer's disease, activation of TFEB has been shown to alleviate pathologies associated with aberrant protein aggregation of β-amyloid and hyperphosphorylated Tau [86–88]. Together, these studies suggest a signaling role for the lysosome in regulating longevity via the mTORC1–TFEB/TFE3 axis, and pose intriguing questions such as whether sensing specific amino acids derived from the lysosome is important for longevity regulation, whether lysosomal amino acid inputs and their detection mechanisms change during the aging process, and whether specific lysosomal amino acid transporters can be pharmacologically targeted for promoting longevity.

Glucose Sensing via AMPK at the Lysosome Surface

To overcome energy and nutrient fluctuation, it is crucial for cells to modulate their metabolic processes accordingly. Disruption of energy balance leads to disease and exaggerates the aging process [89,90]. AMPK is a conserved energy sensor consisting of a catalytic α-subunit and two regulatory subunits, β and γ [91–93]. The γ subunit binds adenosine nucleotide directly and functions as a sensor for low energy status. When the ratio of intracellular ADP:ATP/AMP:ATP increases, AMP/ADP bind to the γ subunit, resulting in the phosphorylation of a crucial residue in the kinase domain of the α subunit, Thr172 [94,95].

Because AMPK activation is a key sensor of nutrient deprivation, it may not be surprising that AMPK is required for longevity conferred by dietary restriction in *C. elegans* and *Drosophila* (Figure 1) [96,97]. AMPK is also required for *C. elegans* lifespan extension upon blockade of glucose metabolism using

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2-deoxy-D-glucose or RNAi knockdown of *gpi-1* encoding glucose phosphate isomerase [98]. Furthermore, overexpression of wild-type or constitutively activated AMPK efficiently increases the lifespan of both worms and fruit flies [97,99].

AMPK was thought to be present only in the nucleus and cytoplasm. However, recent studies show that AMPK also localizes to the late endosome/lysosome through its interaction with AXIN, and organizes specific lysosomal signaling in response to glycolytic signals (Figure 3). AXIN was formerly recognized as a central regulator of the Wnt signaling pathway [100,101]. It was later identified as a scaffold protein driven by AMP to directly tether LKB1, which results in the formation of the AXIN–LKB1–AMPK complex and in turn leads to AMPK activation upon glucose starvation [101]. Subsequently, a yeast two-hybrid screen for AXIN interactors discovered LAMTOR1 as a new AXIN-interacting protein, in addition to its previously established scaffold role within the Ragulator complex in mTORC1 signaling [102]. Further studies suggest that not only LAMTOR1 but also the whole Ragulator and v-ATPase complex contribute to AMPK activation. The v-ATPase–Ragulator complex is likely a docking site for lysosomal translocation of the AXIN–LKB1 complex. The AXIN–LKB1/v–ATPase–Ragulator complex regulates AMPK activation, independently of AMP:ATP/ADP:ATP ratio [103], and instead activates AMPK in response to a specific glycolytic metabolite, fructose-1,6-bisphosphate (FBP), that is derived from glucose catabolism [103]. Among 11 intermediate metabolites in the glycolytic pathway from glucose to pyruvate, only FBP causes the disassociation of AXIN–LKB1 from LAMTOR1 at the lysosomal surface, and its catalytic enzyme aldolase is necessary to prevent AMPK activation [103]. Aldolase is known to interact with v-ATPase, and its binding (but not enzymatic activity) is required for the assembly and activity of v-ATPase [104–106]. Therefore, aldolase can sense FBP at the lysosome, and transmit this glycolytic signal to control the formation of the AXIN–LKB1–Ragulator complex and the lysosomal activation of AMPK. In this case, the lysosome does not directly convert its metabolic status to signal transduction but serves as a platform to localize a specific metabolic reaction and facilitate its coupling with lysosomal signaling. Glucose can also regulate the lysosomal localization of mTORC1 via Rag GTPases in an AMPK-independent manner [40]; however, the underlying mechanism by which Rag GTPase senses glucose levels remains mysterious.

Activated AMPK restores energy homeostasis by switching on ATP-generating catabolic pathways while blocking ATP-consuming anabolic pathways through direct phosphorylation of key substrates in these pathways. For example, phosphorylation of SREBP1 near its proteolytic cleavage site prevents nuclear translocation of this transcription factor and the induction of lipogenesis [107]. In addition, the prolongevity effect of AMPK requires its downstream effectors FOXO/DAF-16 and CRTC/CRTC-1 in *C. elegans* [108]. Phosphorylation of FOXO transcription factor FOXO3 stimulates stress resistance. By contrast, CRTC is retained in the cytoplasm upon phosphorylation by AMPK, which results in suppression of coactivator activity for CREB and inhibits the induction of gluconeogenesis-related targets [109]. Because AMPK shares the same lysosomal tether with mTORC1, AMPK may compete with mTORC1 for activation at the lysosomal surface. Moreover, AMPK can exploit the same downstream effectors of mTORC1, albeit with opposite effects: mTORC1 drives anabolism, whereas AMPK promotes catabolism by directly phosphorylating the ULK1–ATG13–FIP2000 kinase complex to stimulate autophagy [66,110], or by enhancing TFEB activity to induce lysosomal biogenesis [111]. Whether specific substrates are controlled by lysosome-located AMPK or are involved in the regulation of aging remains unclear.

In addition, prolongevity compounds, including metformin and resveratrol, also activate AMPK (Figure 1) [112]. In particular, metformin is a well-known drug that improves glucose homeostasis in type 2 diabetic patients, and its administration promotes longevity and health in *C. elegans* and mice [91,113,114], which is at least partially attributed to lysosomal activation of AMPK [115,116]. It is reported that metformin treatment promotes the formation of the v-ATPase–Ragulator–AXIN/LKB1–AMPK complex at the lysosomal surface, leading to AMPK activation and at the same time turning off mTORC1 activation by dissociating mTORC1 from v-ATPase–Ragulator at the lysosomal surface [116]. Thus, by recruiting either AMPK or mTOR signaling in response to different inputs, the lysosome plays key regulatory roles in metabolism and longevity. Given the great promise of metformin in promoting healthy aging, exploration of other compounds in stimulating the lysosomal activation of AMPK might provide new targets for developing prolongevity

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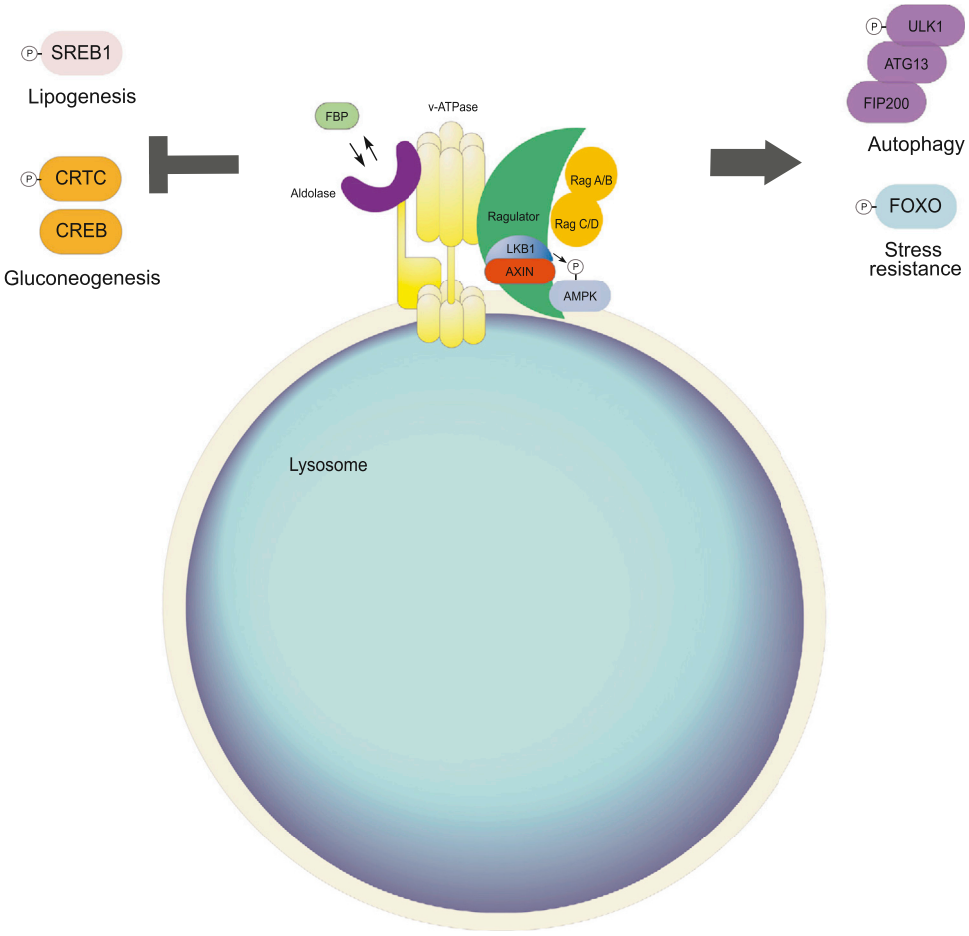

Figure 3. Glucose Sensing by AMPK at the Lysosomal Surface.
Upon glucose depletion, the level of fructose 1,6-bisphosphate (FBP) derived from the glycolysis pathway decreases. The glycolytic enzyme aldolase, which normally binds to the v-ATPase complex in the FBP-loading state on the lysosomal surface, becomes unoccupied upon FBP deprivation. The dissociation of FBP alters the interaction between aldolase and the v-ATPase–Ragulator complex, resulting in the formation of a protein complex consisting of v-ATPase, Ragulator, AXIN, LKB1, and AMPK at the lysosomal surface and activation of AMPK. Activated AMPK phosphorylates (P) multiple downstream substrates, and several examples are listed.

therapies. Future studies in these areas will advance current understanding of AMPK lysosomal signaling in longevity regulation.

Lipid Signaling Derived from Lysosomal Lipases

Lipids are well-known energy fuels and structural building blocks that play important roles in both intracellular and extracellular signaling [117]. The lysosome actively participates in lipid metabolism. Lipids can be delivered to the lysosome by endocytic uptake, autophagy, or cytoplasmic lipid transport proteins. Lipid breakdown is carried out by acid hydrolases such as acid lipases that release free fatty acids from cholesteryl esters and triacylglycerides, acid phospholipases that target phospholipids, acid sphingomyelinases and glycosylceramide-β-gluosidase that generate ceramide from sphingomyelin and glucosylceramide, respectively, and acid ceramidase that converts ceramide into sphingosine [118]. These lysosomal lipid metabolites are then actively transported out of the

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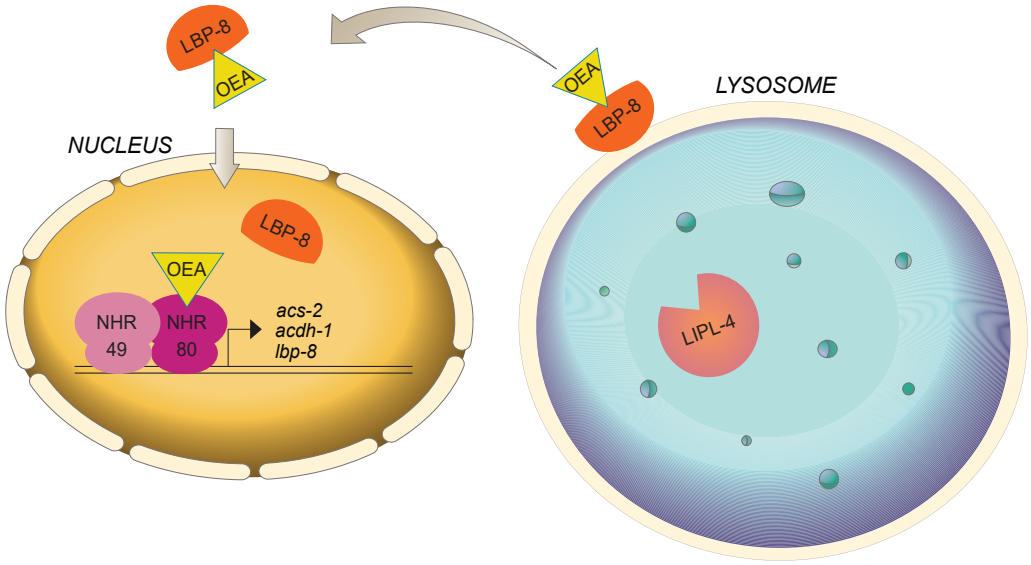

Figure 4. Lysosome-to-Nucleus Lipid Messenger Signaling.
Overexpression of lysosomal acid lipase LIPL-4 induces oleoylethanolamine (OEA) and fatty acid-binding protein LBP-8. Translocation of LBP-8 from the lysosomal surface into the nucleus presents OEA to its nuclear receptor NHR-80, which cooperates with another nuclear receptor, NHR-49, to induce the transcription of target genes such as *lbp-8*, *acs-2*, and *acdh-1*.

lysosome via transport vesicles and exporters [119], and can then participate in mitochondrial oxidation and/or lipogenesis at the endoplasmic reticulum (ER) [120,121]. Recent studies are now revealing the signaling role of lysosomal lipid metabolism in regulating longevity.

The endocytic uptake of LDL particles and the subsequent hydrolysis of cholesteryl esters by lysosomal acid lipase type A (LIPA) is a well-known lipid metabolic process that utilizes the lysosome [122]. Cholesterol generated from this process is not able to freely diffuse out of the lysosome, and requires two exporters, Niemann–Pick type C 1 and 2 (NPC1 and NPC2), to facilitate its transport [119]. A recent discovery couples lysosomal cholesterol inputs with mTORC1 signaling (Figure 2) [123]. Cholesterol can specifically drive the recruitment and activation of mTORC1 at the lysosomal surface, which is mediated by the combination of two transporters, SLC38A9 and NPC1. SLC38A9 can relay cholesterol inputs to stimulate mTORC1 activation via the Ragulator–Rag complex. Specifically, the two tandem cholesterol-recognition motifs (CRAC and CARC) of SLC38A9, but not its arginine-sensing function, are required for this regulation [123]. By contrast, NPC1 binds to SLC38A9 and acts as a negative regulator of mTORC1 by sensing cholesterol depletion [123]. This new cholesterol-dependent mechanism raises interesting questions about how lysosomal amino acid and cholesterol signals cooperate to regulate mTORC1 signaling, whether this mechanism involves specific downstream effectors, and whether longevity regulation by mTORC1 signaling can be attributed to lysosomal amino acid signals, cholesterol signals, or both. Future studies will provide insight into the mechanistic link between lysosomal lipid sensing, lysosomal signaling, and longevity regulation.

In addition to cholesterol, LIPA-induced lipid messenger signaling has also been reported in the regulation of longevity (Figures 1 and 4). Although humans have only one LIPA, *C. elegans* carries nine homologs, LIPL-1 to LIPL-9, and LIPL-1, LIPL-3, and LIPL-4 localize to the lysosome [124–128]. These lysosomal lipases can be induced upon fasting through FOXO/DAF-16- and TFEB/HLH-30-mediated transcriptional control [126,129]. Among them, LIPL-4 is highly induced by several prolongevity mechanisms and is required for their lifespan-extending benefits [85,129]. When overexpressed in the intestine, the fat-storage tissue of *C. elegans*, LIPL-4 is sufficient to promote longevity [125,129]. Induction of LIPL-4 in the lysosome promotes nuclear translocation of LBP-8, a fatty

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acid-binding protein (FABP) in *C. elegans*, which mediates the longevity effect of LIPL-4 [125]. FABPs are a family of 14–15 kDa proteins that can reversibly bind fatty acids and their derivatives, such as endocannabinoid and eicosanoids, and act as lipid chaperones to facilitate the transfer of these hydrophobic substances between different cellular compartments and mediate their metabolic and signaling effects [130]. Specifically, LBP-8 predominantly localizes at the lysosomal surface under normal conditions, and purified LBP-8 proteins bind to several polyunsaturated fatty acids, as well as to monounsaturated oleic acid and its derivative oleoylethanolamide (OEA) with higher affinity [125,131]. Both oleic acid and OEA are sufficient to extend lifespan when supplemented to wild-type worms [125,132], but only OEA is induced upon *lipl-4* overexpression [125]. OEA also acts as an agonist to activate the nuclear hormone receptor NHR-80, which forms a complex with another nuclear hormone receptor, NHR-49. This complex leads to the transcriptional induction of *lbp-8*, thereby forming a positive feedback loop, as well as the transcription of mitochondrial β-oxidation genes to drive lipid catabolism [125,133]. Together, these studies suggest that lysosomal lipid metabolism can actively signal to nuclear transcription, and the shuttling of FABP between the lysosome and the nucleus can mediate this retrograde communication. Future studies to identify proteins facilitating the lysosomal tethering and nuclear transportation of FABP, lysosomal transporters that present lipid messengers to FABP, and other organelles that FABP can signal to will provide additional mechanistic insights into lysosome-to-nucleus retrograde signaling communication, interorganelle crosstalk, and longevity regulation.

Concluding Remarks

The unique position of the lysosome at the intersection between endocytic/phagocytic and autophagic processes makes it a natural fit for integrating extracellular and intracellular inputs and accordingly controlling cellular adaptation. Although the lysosome was long considered to be waste disposal and recycling center, emerging studies support its new role as a platform to initiate, organize, and coordinate diverse signaling events. One mechanism is through direct coupling between lysosomal metabolism and lysosomal signaling, in which specific lysosomal proteins can sense changes in lysosomal metabolism and actively assemble signaling cascades to promote cellular responses. This lysosomal signaling mechanism contributes significantly to the regulation of longevity.

In response to lysosomal signaling, changes in mitochondrial activities, such as mitochondrial dynamics, biogenesis, and β-oxidation, might mediate crucial aspects of cellular adaptation that are required for promoting longevity. First, AMPK activation is sufficient to promote mitochondrial fission. AMPK phosphorylates mitochondrial fission factor [134], which is a mitochondrial outer-membrane receptor for DRP1. DRP1 is required for mitochondrial fission from yeast to mammals [135]. Indirect regulation of DRP1 by AMPK therefore makes it necessary for the longevity effect conferred by AMPK activation [136]. Furthermore, the temporally and spatially controlled overexpression of DRP1 induces mitochondrial fission, which is sufficient to promote longevity in both *C. elegans* and *Drosophila* [137,138]. Second, LIPL-4/LBP-8-mediated lysosomal lipid signaling induces mitochondrial fatty acid β-oxidation, which drives metabolic reprogramming toward lipid catabolism, and reduces the activity of mitochondrial electron transport chain complex II, leading to increased production of mitochondrial reactive oxygen species (mtROS) and activation of mtROS-mediated transcription of antioxidant genes [133]. In this way, lysosomal lipid messenger signaling can actively tune mitochondrial activity to coordinate lipid metabolism, redox homeostasis, and longevity. Last, TFEB activation upregulates PGC1α, a master regulator of mitochondrial biogenesis, and cooperates with nuclear receptor PPARα to promote mitochondrial β-oxidation [77]. Increased mitochondrial β-oxidation of fat storage tissues is known to prolong lifespan in *C. elegans* [133]. Thus, one area for future studies will be to systematically understand how lysosomes interact with mitochondria, the nucleus, and other cellular compartments both physically via membrane contact and functionally via signaling mechanisms (see Outstanding Questions).

In recent years, emerging studies have provided exciting discoveries regarding the signaling role of the lysosome. We have started to scratch the surface of the complex lysosomal signaling network which integrates lysosomal luminal metabolism and its derived metabolic products,

Outstanding Questions

Are there specific metabolites derived from lysosomes that are important for longevity regulation?

Are lysosomal signals and their detection mechanisms affected by aging?

Can AMPK directly respond to glycolytic metabolites derived from lysosomal metabolism?

What lysosome-derived metabolites signal through mTORC1 and AMPK?

What are the specific substrates downstream of AMPK and mTORC1 lysosomal activation, and what are their effects on aging and longevity?

What are the specific transporters for signaling metabolites derived from lysosomal metabolism, and how do they cooperate with lysosomal signaling activation?

Can specific metabolite transporters at the lysosomal surface be pharmacologically targeted for promoting longevity?

What proteins facilitate the lysosomal tethering and nuclear transportation of FABP?

Are additional FABPs or lysosome signaling molecules required for long-range interorganelle or even intertissue communication in longevity regulation?

How do lysosomes interact with mitochondria, the nucleus, and other cellular compartments both physically via membrane contact and functionally via signaling mechanisms? How does this interorganelle crosstalk change with increasing age?

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sensors/transporters at the lysosome surface, and factors transducing and receiving lysosomal signals in the cytoplasm and other organelles. High-throughput proteomic and metabolomic analyses of lysosomes are making inroads in discovering new lysosome-derived metabolic cues and their associated sensing and signaling mechanisms [139]. This developing area will continue to elucidate new lysosomal signaling mechanisms and their contribution to the maintenance and improvement of cellular homeostasis and organismal fitness, as well as providing new regulatory modes and therapeutic targets for promoting healthy aging.

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