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REVIEW

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A lysosome-centered view of nutrient homeostasis

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ABSTRACT

Lysosomes are highly acidic cellular organelles traditionally viewed as sacs of enzymes involved in digesting extracellular or intracellular macromolecules for the regeneration of basic building blocks, cellular housekeeping, or pathogen degradation. Bound by a single lipid bilayer, lysosomes receive their substrates by fusing with endosomes or autophagosomes, or through specialized translocation mechanisms such as chaperone-mediated autophagy or microautophagy. Lysosomes degrade their substrates using up to 60 different soluble hydrolases and release their products either to the cytosol through poorly defined exporting and efflux mechanisms or to the extracellular space by fusing with the plasma membrane. However, it is becoming evident that the role of the lysosome in nutrient homeostasis goes beyond the disposal of waste or the recycling of building blocks. The lysosome is emerging as a signaling hub that can integrate and relay external and internal nutritional information to promote cellular and organismal homeostasis, as well as a major contributor to the processing of energy-dense molecules like glycogen and triglycerides. Here we describe the current knowledge of the nutrient signaling pathways governing lysosomal function, the role of the lysosome in nutrient mobilization, and how lysosomes signal other organelles, distant tissues, and even themselves to ensure energy homeostasis in spite of fluctuations in energy intake. At the same time, we highlight the value of genomics approaches to the past and future discoveries of how the lysosome simultaneously executes and controls cellular homeostasis.

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Introduction

The presence of approximately 60 different hydrolases makes the lysosome the primary catabolic center of the cell.[1] The products of digestion are ultimately used as building blocks for biosynthetic pathways or to meet energy demands. Lysosomal membrane proteins include exporters of these metabolites allowing their translocation and clearing.[2] With the collective action of lysosomal hydrolases that include proteases, glycosidases, lipases, nucleases, phosphatases and sulfatases, macromolecules and even metabolic organelles such as mitochondria and peroxisomes or energy storage compartments such as lipid droplets can be degraded or recycled in the lysosome.[3,4] However, because it is the only organelle receiving cargo directly from both the inside and the surroundings of the cell, the lysosome is uniquely positioned to have the additional functions of integrating nutritional information and orchestrating homeostatic responses. In fact, as it gains more attention, the multifaceted and central role in nutrient homeostasis of this formerly neglected organelle becomes increasingly evident. Although there are many essential functions ascribed to the lysosome, here we focus on 3 interrelated but distinct functions relevant to nutrient homeostasis. The first section, "Nutrient sensing at the lysosome," describes the emerging role of the lysosome in sensing nutrients and locally relaying information to the master nutrient sensors MTOR and AMPK. In section 2, "Nutrient processing by the lysosome," although we acknowledge the lysosome's role as a processor of damaged organelles, macromolecular complexes, nutrient and growth factor receptors, and proteins, we focus on the role of lysosomal hydrolases in processing energy-dense molecules (glycogen and lipids) to generate energy units that contribute to energy homeostasis. The third section, "Nutrient signaling from the lysosome," summarizes the role of the lysosome in generating signaling molecules capable of traveling either to the nucleus to activate homeostatic transcriptional programs, or to distant tissues to activate global homeostatic responses. All in all, we describe a picture in which the lysosome plays a central role in providing nutrients and ensuring that organisms invest in growth and reproduction only when the internal and external conditions are favorable to do so.

Nutrient sensing at the lysosome

A key nutrient-sensing node acting in all tested eukaryotes is the kinase complex MTOR complex 1 (MTORC1). This master growth regulator promotes anabolic processes such as protein

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translation when nutrients are available, and licenses catabolic processes such as macroautophagy when nutrients are scarce.[5] Interestingly, nutrients such as amino acids[6] and glucose,[7] promote the translocation of MTORC1 to the lysosomal surface. Proteomics approaches revealed that in the presence of nutrients, 2 protein complexes, the Ragulator and the RAG-heterodimer, dock MTORC1 on the surface of the lysosome, and that formation of this multiprotein complex, coined *ly*sosome *nu*trient *s*ensing machinery or LYNUS,[8] is a key event in nutrient signaling through MTORC1.[9,10] Ragulator is a multiprotein guanine nucleotide exchange factor (GEF) that acts as a lysosomal anchor for RAG.[6,9] RAG is a multiprotein complex comprising the obligate GTPase heterodimers RRAGA or RRAGB in complex with RRAGC or RRAGD. MTORC1 seems to be differentially regulated by specific amino acids.[11] The human SLC38A9 (solute carrier family 38 member 9) is part of the Ragulator-GTPase machinery,[12] and activates MTOR in the presence of arginine.[13] RRAGA and RRAGB are required for MTOR activation by leucine, whereas glutamine does not require RAG GTPases. Instead glutamine-mediated MTORC1 activation occurs via the ARF1 (ADP ribosylation factor 1) GTPase.[11]

Various proteins interact with Ragulator and RAG GTPases to facilitate and fine-tune MTOR-mediated responses at the lysosome. For example, a Ragulator interacting protein, BORCS6/c17orf59, was recently shown to competitively inhibit RAG binding to the Ragulator, thus preventing RAG GTPase docking to lysosomes, and negatively affecting the amino acid activation of MTORC1.[14] However, a loss of BORCS6 in HeLa cells has no effect on the inhibition of MTORC1 signaling during nutrient deprivation suggesting that there could be other roles for the Ragulator-BORCS6 complex independent of MTORC1. BORCS6 may regulate the interaction of Ragulator with BORC, shown to be important for lysosomal positioning.[15] Another MTOR modulator is SQSTM1/p62 (sequestosome 1), a multidomain receptor protein involved in intracellular signaling, which interacts with MTORC1 in the presence of amino acids. This interaction is in turn required for the interaction of MTORC1 with RAG GTPases, and thus the translocation of MTORC1 to the lysosomal surface.[16] Also, SQSTM1 interacts with TRAF6 (TNF receptor associated factor 6), which is required for the activation of MTOR.[17] In addition, the GATOR complex (*G*TPase *a*ctivating protein *to*ward *R*ag GTPases), a multiprotein complex consisting of 2 subcomplexes, GATOR1 (DEPDC5-NPRL2-NPRL3) and GATOR2 (MIOS-SEH1L-WDR24-WDR59-SEC13), regulates the RAG GTPases.[18,19] GATOR1 functions as a GTPase activating protein for RRAGA and RRAGB, and GATOR2 acts as a negative regulator of GATOR1.[18] Finally, a series of stress responsive growth regulators known as sestrins (SESN1, SESN2, and SESN3) interact with GATOR2 in response to lack of amino acids. Sestrins act as guanine nucleotide dissociation inhibitors for RAG GTPases, thus suppressing the lysosomal localization of MTOR.[20-22]

A *Drosophila* cell-based RNA interference screen for genes involved in lysosomal biogenesis or function, unveiled that amino acid signaling to MTORC1 does not begin at the plasma membrane, but begins within the lysosome.[23] The vacuolar-type H^+ adenosine triphosphatase (V-ATPase), an ATP-dependent proton pump, has a pivotal role in acidifying the lysosomal lumen by pumping protons into the lysosome. However, V-ATPase regulates signaling through MTOR independently of its acidifying capacity.[23] Assembly of 2 domains of the V-ATPase, the membrane spanning proton-translocating domain (V_0) and the peripheral ATPase domain (V_1) is increased upon amino acid starvation, but reversed on re-addition of amino acids. Amino acid-triggered changes in V-ATPase assembly also depend on its catalytic activity as well as the pH of the lysosomal lumen.[24] In the presence of amino acids, V-ATPase triggers Ragulator GEF activity for RAG GTPases.[9] Interestingly, recruitment of MTOR to the lysosome is dependent on RRAGA/B but seems to be independent of RAG GTP charge.[10,25,26]

Although how nutrient sufficiency leads to recruitment of MTORC1 to the lysosomal surface is not fully understood, lysosomal localization and interaction with its activator RHEB are required for full MTOR activation. The small GTPase RHEB (Ras homolog enriched in brain), stimulates the phosphorylation and activation of MTORC1 when bound to GTP in a nutrient-abundant state. Upon amino acid withdrawal or the inhibition of growth factor signaling, RAG GTPases recruit TSC (tuberous sclerosis complex) to the lysosomes.[27] TSC, which acts as a GTPase-activating protein for RHEB, is composed of TSC1, TSC2, and the GTPase TBC1D7, which converts GTP-RHEB to GDP-RHEB preventing its stimulatory effect on MTORC1 (Fig. 1).[28,29] The GTP/GDP-independent activation of MTORC1 by RHEB may implicate other modulators in RHEB-mediated activation of MTORC1.[30]

In addition to nutrients, metazoans couple growth rates to growth factors. Notably, insulin-mediated activation of MTORC1 requires amino acids and Ragulator present on the lysosomal surface.[6,25] Insulin and growth factors stimulate the class I phosphoinositide 3-kinase (PI3K), which phosphorylates AKT. In turn, AKT phosphorylates TSC2 of the TSC complex.[31-33] In the absence of growth factors, the TSC complex is localized to the lysosome in a RHEB-dependent manner. In response to insulin and AKT-mediated phosphorylation, the TSC complex gets acutely released from lysosomes eventually leading to MTORC1 activation.[34] Thus, the lysosome is a nexus between nutrients, growth factors, and MTORC1-mediated regulation of cellular and organismal growth.

Glucose regulates MTORC1 activity through its regulation of RHEB. The enzyme GAPDH (glyceraldehyde-3-phosphate dehydrogenase), directly interacts with RHEB independent of GDP/GTP-RHEB binding when glucose levels are low, thereby preventing RHEB from activating MTORC1.[35] Knocking down or perturbing the interaction between GAPDH and RHEB renders MTORC1 unable to sense changes in glucose levels. Interestingly, this GAPDH-RHEB interaction is observed even under high levels of glucose suggesting that GAPDH shuttles between glycolysis and the MTOR pathways acting as a direct mediator of MTORC1 signaling in response to glucose levels. Low glucose levels also affect MTORC1 signaling indirectly through decreasing ATP levels, which leads to activation of AMP-activated protein kinase (AMPK). AMPK inhibits MTORC1 activity by phosphorylating TSC2, which inhibits RHEB-mediated MTORC1 activation.[36,37] The RHEB-mediated signaling of glucose to MTORC1 suggests that lysosomal

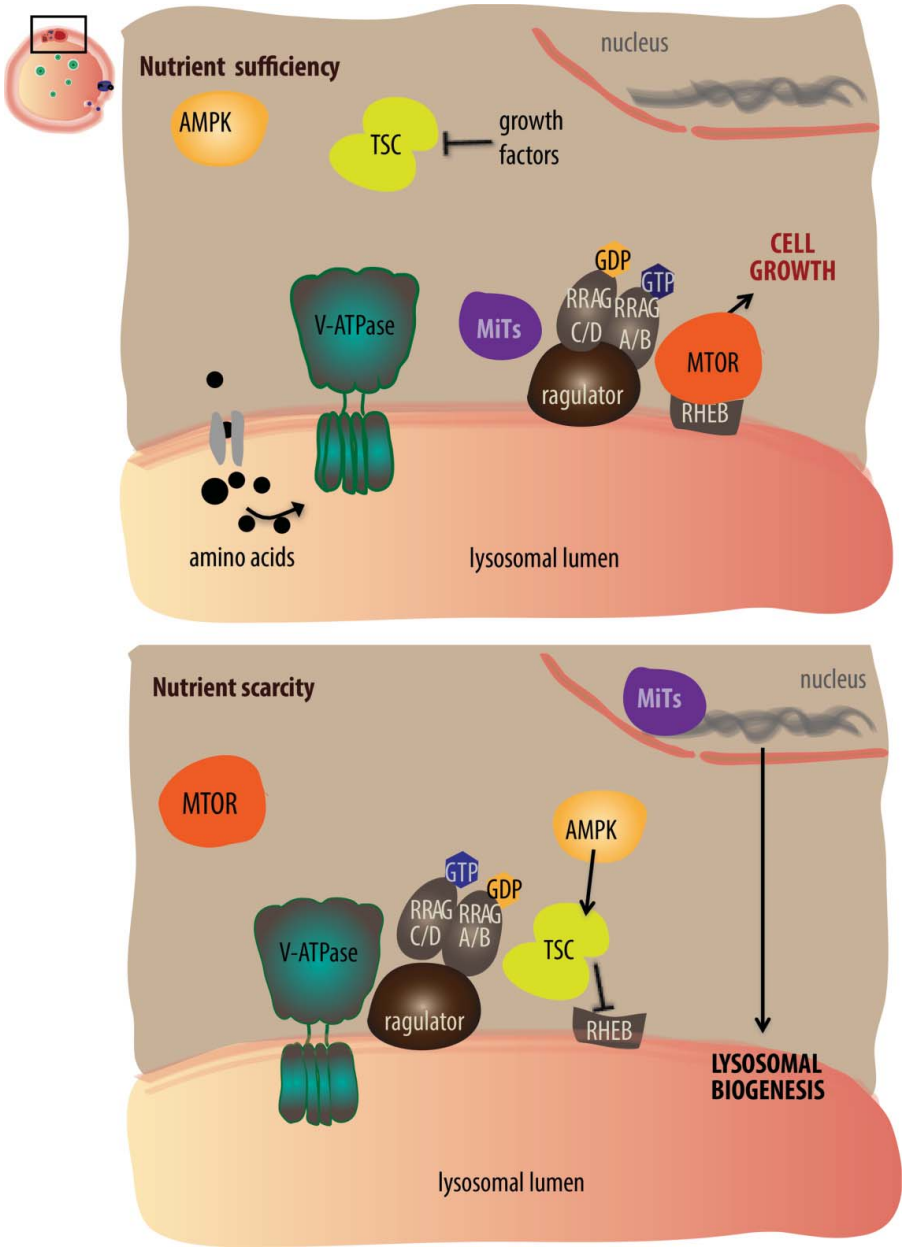

Figure 1. The lysosome is a nutrient-sensing center. When nutrients are sufficient (upper panel), amino acids induce structural changes in the lysosomal vacuolar-type ATPase (V-ATPase), so that it weakens its association with the Ragulator-RAG complex. Thus, Ragulator-RAG can recruit MTOR to the lysosomal membrane.[23] The small GTPase RHEB that resides at the lysosomal membrane, can now stimulate the phosphorylation and consequent activation of MTOR.[28,29] RRAGA/B facilitates MTOR activation and recruitment of TFEB to the lysosome for its phosphorylation and retention in the cytoplasm by YWHA chaperones.[9,26,47] When nutrients are scarce (bottom panel), the RAG GTPases recruit TSC (tuberous sclerosis complex), which converts GTP-RHEB to GDP-RHEB causing inactivation and release of MTOR into the cytosol.[27] Fasting stimulates AMPK, which in turn activates the TSC complex. In addition, since MTOR phosphorylates the MiTs transcription factors, upon MTOR inhibition, these transcriptional regulators are not phosphorylated and are free to translocate to the nucleus and activate genes involved in lysosomal biogenesis and function.[46,48,50,51]

localization would also be an important component of glucose sensing; however, this has so far not been directly tested. Whether or not MTORC1 relocates to the cytoplasm when inactivated by GAPDH-RHEB signaling remains to be determined.

Lipids also interact with and regulate MTOR activity. The saturated free fatty acid palmitate induces MTORC1 activation by increasing its translocation onto the lysosomal surface.[38] Palmitate supplementation also decreases AMPK phosphorylation leading to hypophosphorylation of RPTOR and the activation of MTORC1; this is reversed upon addition of the monounsaturated fatty acid oleate.[39] Oleate and the polyunsaturated fatty acid eicosapentanoic acid, inhibit MTORC1 activation.[38] Thus, saturated and unsaturated FFAs could have opposing effects on MTORC1 regulation.

AMPK is another major intracellular energy sensor that can inhibit MTORC1 by direct phosphorylation of RPTOR[40] or by activating TSC2.[41] The V-ATPase-Ragulator complex also plays a role in sensing low energy levels by forming a complex with the AMPK regulators AXIN and STK11/LKB1 at the lysosome, and subsequent activation of AMPK. In addition, the GEF activity of Ragulator for RAG is inhibited by AXIN,

leading to inactivation of MTOR and thus activation of the catabolic activities of the cell.[42] Therefore, the lysosome is not a passive loading dock for important nutrient sensors; instead, the lysosome is sensing and relaying information to warrant that the cell will fully commit to growth only when long-range growth factor signals, local building blocks, and energy are present.

The location of the lysosome in the cell is also found to be important in coordinating catabolic and anabolic processes that respond to nutrients. When nutrients are not limiting, lysosomes are found at the periphery of the cell associated with an activated MTORC1. By contrast, starvation causes perinuclear clustering of lysosomes facilitating autophagosome-lysosome fusion and the consequent release of nutrients during starvation.[43]

An emerging line of investigation in lysosomal biology is how lysosomal biogenesis, function, and turnover are regulated through the lysosome. Integrated transcriptomics analysis revealed that several genes encoding lysosomal proteins are co-expressed after genetic, chemical, or environmental perturbations.[44] Promoter analysis of these lysosomal genes revealed a common regulatory sequence known as an E-box.[45] Together these data led to the identification of the coordinated lysosomal enhancement and regulation (CLEAR) gene network, which controls lysosomal biogenesis, and lysosome-related functions such as autophagy, exocytosis, endocytosis, and phagocytosis. The related E-box transcription factors MITF (microphthalmia-associated transcription factor), TFE3 (transcription factor binding to IGHM enhancer 3), TFEC (transcription factor EC), and TFEB (transcription factor EB) can bind to CLEAR sites. MITF, TFE3 and TFEB, hereafter MiTs, respond to starvation promoting autophagosome formation and lysosomal biogenesis.[46-48] When MTORC1 is active, it phosphorylates MiTs. Given that active MTOR is on the lysosomal membrane, the MiT transcription factors must be recruited to the lysosome to be phosphorylated. MiTs transiently localize to the lysosomal membrane through binding to the same RAG GTPases that recruit MTORC1 to the lysosome. Phosphorylation causes their binding to the cytosolic chaperone YWHA/14-3-3 and sequestration in the cytoplasm.[46-50] The current model suggests that in fed conditions the MiT transcription factors continuously cycle between the lysosome and the cytosol. When MTORC1 is inhibited, unphosphorylated MiTs are released from the YWHA chaperones and are free to enter the nucleus to transcriptionally regulate lysosomal homeostasis and autophagy.[46,48,51] Additionally, the class III phosphatidylinositol 3-kinase PIK3C3/VPS34 (a pro-autophagic lipid kinase) controls lysosomal tubulation downstream of MTOR. Upon phosphorylation by MTORC1, UVRAG activates PIK3C3; mutant versions of UVRAG result in reduced PIK3C3 activity, which in turn reduces the lysosomal pool of phosphatidylinositol 3-phopshate (PtdIns3P) causing increased lysosomal tubulation and failure to generate normal lysosomes during starvation.[52] Therefore, through the control of MTORC1, lysosomes control their own biogenesis and function.

Various ion channels present in the lysosomal membrane also help sense the presence of nutrients. MTORC1 associates with an ATP-sensitive sodium channel, a complex of TPCN1 and TPCN2 (2 pore segment channels) on the lysosomal membrane. Upon nutrient depletion and reduced ATP, MTORC1 is translocated away and the channel is open. This channel controls membrane potential, pH stability, and amino acid homeostasis.[53] The activity of a lysosomal Ca^{2+} channel, MCOLN1 (mucolipin 1) is also increased during starvation. Increased Ca^{2+} release promotes autophagosome-lysosome fusion as well as lysosome reformation from autolysosomes.[54] A lysosome specific phosphoinositide PtdIns(3,5)P_2, activates both ion channels, TPCN and MCOLN1.[55,56] Thus, regulation of lysosomal cation channels is another mechanism by which lysosomes control their own health and abundance.

Nutrient processing by the lysosome

In this section we focus on the role of the lysosome in digesting energy-dense substrates like glycogen and lipids, and make a brief reference to the processing of proteins, growth factors and their receptors, micronutrients, and metabolic organelles. For a comprehensive description of lysosomal storage disorders, refer to recent reviews on the subject.[57,58]

In addition to its role in nutrient sensing, the lysosome contributes to energy homeostasis through its direct role in the mobilization of energy stores. Specialized lysosomal hydrolases process energy-rich molecules such as lipids and glycogen to generate energy units and building blocks. Lysosomal hydrolases digest and mobilize nutrients in growth-promoting conditions (fed state), as made evident by the hyper-accumulation of undigested lipids or glycogen when the function of the lysosomal hydrolases is impaired, or of digested products when these cannot be cleared via lysosomal membrane transporters or other unknown exporting mechanisms. Undigested lipids or glycogen accumulate inside the lysosome and become toxic, leading to pathological states ranging from mild disease to death.[59,60] The essential role of the lysosome in nutrient homeostasis is illustrated by the compromised survival observed in organisms with impaired lysosomal hydrolase activity; this selective pressure has led to a high level of conservation of the hydrolases and their modulators across eukaryotes (Table 1).

The enzyme GAA (glucosidase, α; acid) is responsible for breaking down glycogen into glucose within the lysosome, and mutations in this gene lead to Pompe disease.[59] Pompe disease is characterized by the accumulation of glycogen within and beyond the lysosome, most prominently in glycogen-storing tissues like skeletal and cardiac muscle.[61] Humans with penetrant mutations in GAA experience severe muscle weakness in skeletal and respiratory muscles, and many die as infants.[62] Additionally, the disrupted mobilization of sugars from the lysosome can also lead to disease, as is the case in Salla disease, a sialic acid storage disease, where export of the monosaccharide sialic acid is defective due to mutations in its transporter, SLC17A5/sialin.[63] It is unclear how glucose is transported from the lysosome to the cytoplasm to be processed through the glycolytic pathway. Of the 3 sugar transporters that have been described to reside in the lysosome, only one has been shown to transport glucose out of rat liver lysosomes.[64,65] More recently, SLC2A8/GLUT8 (solute carrier family 2 [facilitated glucose transporter], member 8) was found to contain a highly conserved late endosomal/lysosomal motif. SLC2A8 was

Table 1. The lysosome is an essential energy generator.

Macromolecule	Defective gene/ protein	*S. cerevisiae*	*C. elegans*	*M. musculus*	*H. sapiens*
Glycogen	GAA (glucosidase, α; acid)	Glycogen accumulation[119]	Protein conserved[120] but phenotype not reported	Increased glycogen content in cardiac and skeletal muscle[121]	Pompe disease: general myopathy, cardiomyopathy, pulmonary failure[122-124]
Triglycerides and cholesteryl esters	LIPA (lipase A, lysosomal acid, cholesterol esterase)	Increased steryl ester content[79]	Increased fat mass[77]	Massive ectopic fat accumulation, shortened life span[125]	CESD and Wolman disease: massive ectopic fat accumulation, mild symptoms to infant death[126]

The essential, and consequently conserved, role of lysosomal hydrolases in providing energy units by processing energy-dense nutrients is illustrated here by the phenotypic effects of their mutation in eukaryotes ranging from yeast to humans. CESD, cholesteryl ester storage disease.

observed within endosomal/lysosomal membranes, and it does not translocate to the plasma membrane like the better-known transporter SLC2A4/GLUT4; however, the functional relevance of SLC2A8 remains to be determined.[66]

Unlike glucose, which is soluble in the bloodstream and internalized into the cytoplasm through dedicated transporters, lipids circulate as parts of various lipoproteins and are taken up from the extracellular environment through specialized internalization mechanisms.[67] In one of the best-known examples, receptor-mediated endocytosis mediates the uptake of low-density lipoprotein (LDL) particles and directs them to the lysosome.[68] First, LDL binds the LDL receptor, then the plasma membrane invaginates forming a clathrin-coated vesicle containing LDL bound to its receptor, and these vesicles eventually fuse with the lysosome.[67] Within the lysosome, LIPA (lipase A, lysosomal acid, cholesterol esterase) is responsible for hydrolyzing triglycerides and cholesteryl esters contained in the LDL particle, converting them into free fatty acids and cholesterol.[69,70] The lysosome membrane protein NPC1 (Niemann-Pick disease, type C1), deletion of the gene that causes Niemann-Pick disease, type C, facilitates the efflux of cholesterol out of the lysosome.[71,72] It is unclear how free fatty acids are transported from the lysosome to the mitochondria, or the mitochondria and peroxisomes in the case of lower eukaryotes for their processing through β-oxidation.

In addition to processing bloodstream-circulating lipids, the lysosome digests lipids stored in cytoplasmic lipid droplets. Lipid droplet hydrolysis in fasted hepatocytes occurs mainly in autolysosomes, a process termed lipophagy.[73] When cells are under nutritional stress, the small GTPase RAB7A is activated and promotes trafficking of lipid droplets to multivesicular bodies and lysosomes for lipophagy.[74] Once in the lysosome, lipids are broken down by specialized lipases. Lysosomal acid lipases[75] and Atg15,[76] an autophagy-related protein with predicted triglyceride-lipase activity, are proposed to mediate lipophagy. Epistatic analyses were used to establish that lysosomal lipases are responsible for breaking down fats through lipophagy in *C. elegans*. *C. elegans* mutants for the lysosomal lipase genes *lipl-1* and *lipl-3* accumulate 2-fold more fat than wild-type animals, and this obesity phenotype is not additive with the genetic inactivation of autophagy.[77] High-content in vivo RNA interference screening in *C. elegans* revealed that the MAX-like transcription factor MXL-3 represses lysosomal lipolysis in the presence of nutrients. MXL-3 shares its target sequence with HLH-30 (the *C. elegans* TFEB ortholog).[78] Opposite of MXL-3, HLH-30 induces the expression of lysosomal lipase genes upon fasting and this response is conserved in mouse and human cells in culture.[77] Interestingly, whereas mammals have only one lysosomal acid lipase, LIPA, yeast defective in either *ATG15* or *TGL1* (the homolog of human LIPA) accumulate more lipid droplets and mobilize lipids at a slower rate.[79] *C. elegans* has at least 3 lysosomal acid lipases.[77,80] This higher functional divergence in the lysosome of lower organisms suggests a need for more specialized processing, possibly to distinguish nutrients from lipid signals and biotoxins abundant in the complex habitats of these organisms. Mice deficient in lysosomal acid lipase show massive storage of triglycerides and cholesteryl esters in adult liver, adrenal glands, and small intestine, and die at 7 to 8 mo of age.[81] In humans, lysosomal acid lipase deficiency causes cholesteryl ester storage disease and the more severe Wolman disease, which is characterized by infant mortality accompanied by increased fat stores.[60]

Two additional roles for the lysosome in lipid homeostasis were recently reported. Mice with impaired chaperone-mediated autophagy (CMA), a chaperone-dependent targeting of soluble cytosolic proteins to the lysosome, show liver steatosis in the presence of functional macroautophagy, suggesting that CMA is involved in lipid droplet breakdown.[82] Like macroautophagy, CMA is activated during prolonged starvation.[83] However, as expected from the consensus that the main substrates of CMA are proteins and not lipids, the role of CMA in lipid homeostasis is mediated by the proteolytic and not the lipolytic function of the lysosome. PLIN2 (perilipin 2) and PLIN3 are lipid droplet-coating proteins that protect lipid droplets from cytosolic lipases such as LIPE (lipase, hormone-sensitive). In basal conditions, and more so upon fasting, CMA translocates PLIN2 and PLIN3 to the lysosome for their degradation. Therefore, the lysosomal degradation of perilipins promotes fat breakdown by licensing cytosolic lipases access to their substrates contained in lipid droplets.[84] Second, recent data suggest that the lysosome could also be involved in scavenging of lipids for long-term provision of energy during prolonged starvation.[85]

The lysosome also stores and provides nutrients, generates building blocks (i.e., amino acids), recycles nutrient and growth factor receptors, and participates in the quality control for important metabolic organelles. Proteins delivered to the yeast

equivalent of the lysosome, the vacuole, are degraded by proteases and other vacuolar hydrolases.[86] Newly recycled amino acids such as leucine are effluxed to the cytosol via various vacuolar effluxers including Atg22, enabling protein synthesis.[87] Lysosomal proteases can nonselectively digest endogenous or exogenous proteins. Lysosomal proteases are generally termed cathepsins, which are mainly cysteine and aspartic proteases. Cathepsins are differentially active in various cell types and tissues, providing some level of substrate specificity.[88-90] Additionally, mammals break down cytosolic proteins selectively delivered to the lysosomes through CMA. The cytosolic HSPA8/HSC70 chaperone (heat shock protein family A [Hsp70] member 8) recognizes proteins containing a sequence similar to KFERQ.[91] These complexes formed of CMA substrate bound to HSPA8 bind to LAMP2A (lysosomal-associated membrane protein 2A) promoting its multimerization. CMA substrate proteins undergo unfolding and pass through the LAMP2A multimers helped by intralysosomal HSPA8. Lysosomal proteases then degrade the protein substrates after translocation.[92] Disease can arise from the improper breakdown or efflux of protein-derived amino acids from the lysosome. For example, an amino acid transporter called CYNS/cystinosin helps the translocation of cysteine across the lysosomal membrane; deletion of the corresponding gene leads to cystinosis, a lysosomal storage disease.[93] In *C. elegans*, loss of the lysosomal lysine/arginine transporter LAAT-1 causes accumulation of lysine and arginine and results in enlarged and defective lysosomes that compromise embryonic development.[94] Lysosomes are not only involved in digesting nutrients but also in temporarily storing essential elements such as zinc or iron.[95,96]

In addition to the mobilization of macro- and micronutrients, the lysosome processes critical growth factors, and growth factor-receptor complexes. GHR (growth hormone receptor) bound to GH1 (growth hormone 1) is degraded in the lysosome after selective delivery of the receptors that will be recycled back to the plasma membrane.[97] Inhibition of the sorting of EGFR (epidermal growth factor receptor) into multivesicular bodies and its subsequent degradation in the lysosome leads to tumorigenesis in mice, developmental defects in *Drosophila*, as well as vulval abnormalities in *C. elegans*.[98-100] In addition, secretory granules containing growth factors such as insulin are also processed in the lysosome.[101] Therefore, lysosomal degradation of growth factors and their receptors contributes to fine tuning cellular responses to growth signals.

The lysosome is also required for the rejuvenation of metabolic organelles. In yeast, selective digestion of the endoplasmic reticulum happens in the vacuole during excessive ER stress. Termed reticulophagy/ER-phagy, this mechanism is distinct in that it does not require autophagosomes or proteins implicated in autophagy.[102] Additionally, the lysosome degrades mitochondria brought to it through a specialized form of macroautophagy termed mitophagy.[103] Lysosomes also recycle ribosomes,[104] peroxisomes,[105] and even other impaired lysosomes.[106]

Long-range nutrient signaling from the lysosome

Significant progress has been made in our understanding of the role of the lysosome in providing a platform and local signaling to MTORC1 and AMPK. By contrast, little is known about the contribution of the lysosome to distal signaling. However the few known examples, described below, suggest the lysosome generates short- and long-range signals with important roles in cellular and organismal homeostasis.

As described in section 2, cholesteryl esters are taken up by receptor-mediated endocytosis, and degraded through the action of LIPA to release cholesterol through specialized transporters. In addition to being a precursor of many metabolites and a structural component of membranes, cholesterol released from the lysosomes also functions as a signaling molecule. The SREBF (sterol regulatory element binding transcription factor) proteins control the expression of genes involved in lipid uptake and biosynthesis.[107] When lysosome-derived cholesterol levels are high, SREBF resides in the ER, bound to SCAP (SREBF chaperone) and INSIG1 (Fig. 2).[108-110] Low cholesterol levels lead to dissociation of INSIG1, freeing the SREBF-SCAP complex to traffic to the Golgi where it is cleaved by the proteases MBTPS1/S1P and MBTPS2/S2P. Free SREBF translocates to the nucleus to activate the transcription of genes involved in lipid uptake and biosynthesis.[110] Conversely, binding of cholesterol to SCAP inhibits cleavage of the SREBF-SCAP complex. In this way, lysosomal cholesterol represses its own synthesis. Additionally, an excess of lysosome-derived cholesterol causes activation of the transcription factor NR1H/LXR (nuclear receptor subfamily 1 group H), which transcribes genes involved in the removal of cholesterol from cells.[111] Thus, sterol signals originated in the lysosome are an integral part of cholesterol homeostasis.

In fed as well as in starvation conditions, lipids stored in lipid droplets and the membranes of organelles are processed in the lysosome. Lysosomal acid lipases then break down these lipids into fatty acids. Mammals have a single lysosomal lipase, LIPA, whereas other animals like *C. elegans* have several lipases within their lysosomes. In *C. elegans*, the lysosomal acid lipase gene *lipl-4* is upregulated upon starvation.[112] Increased expression of LIPL-4 leads to an enrichment in ω-3 and ω-6 polyunsaturated fatty acids during starvation,[112] and oleoylethanolamide (OEA) in nonphysiological conditions.[80] Both ω-3 and ω-6 polyunsaturated fatty acids (PUFAs) and OEA act as lipid signals. The lipid binding proteins LBP-3 and LBP-5, whose encoding genes are also upregulated upon fasting, transport ω-3 and ω-6 PUFAs to distant tissues where they activate autophagy in response to nutrient deprivation.[112] Lapierre et al. reported that upregulation of LIPL-4 leads to the inactivation of LET-363/MTOR;[113] it would be interesting to test if supplementation of the diet with ω-3 and ω-6 PUFAs is sufficient to reduce MTOR activity and thus explain the beneficial effects of fish oils on health span. Folick et al. reported a more intriguing lipid signaling mechanism by which the lipid binding protein LBP-8, whose encoding gene is paradoxically downregulated upon fasting,[112] translocates OEA into the nucleus.[80] OEA then binds and activates the nuclear hormone receptors NHR-49 and NHR-80; that among others, regulate the expression of genes involved in fatty acid β-oxidation (Fig. 2). Interestingly, in MCF-7 breast cancer cells, ω-3 PUFA-derived ethanolamines stimulate the mammalian homolog of NHR-49, PPARG/PPARγ (peroxisome proliferator-activated receptor gamma), inhibit the

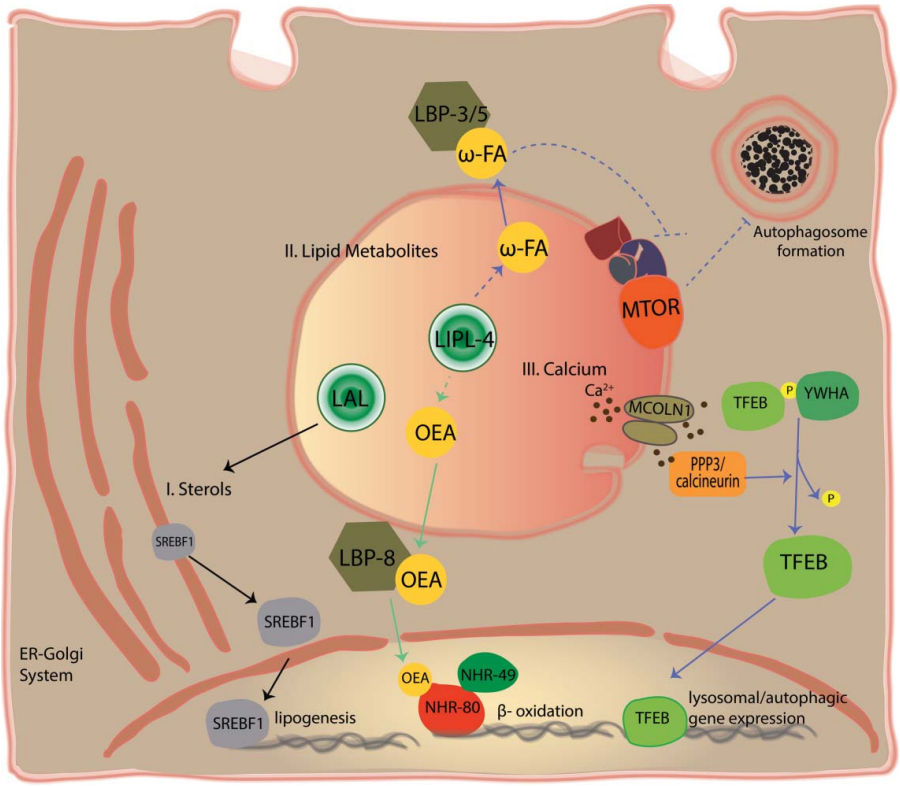

Figure 2. Long-range signals from the lysosome coordinate nutrient homeostasis. The lysosome generates signals that travel to activate cell autonomous or systemic responses that promote nutrient homeostasis. Some of these signaling pathways are depicted here: I. Cholesterol uptake and synthesis is controlled from the lysosome. Cholesterol is taken up and processed by the lysosomal system. When the lysosome releases enough cholesterol, the transcription factor SREBF/SREBP is in the ER. By contrast, low cholesterol promotes SREBF trafficking from the ER to the Golgi (not shown), and then to the nucleus where it transcribes genes involved in lipid uptake and biosynthesis.[110] II. Lysosome fatty-acid derivatives distally control autophagy and the transcription of β-oxidation genes. In *C. elegans*, fasting leads to increased lysosomal lipase activity (LIPL-4).[112] Increased LIPL-4 activity is capable of: 1) generating lipid signals including ω-3 and ω-6 polyunsaturated fatty acids (ω-FA) and oleoylethanolamide (OEA),[80,112] 2) inhibiting LET-363/MTOR,[113] 3) activating autophagy,[112,113] and 4) inducing β-oxidation and other metabolic genes through NHR-49 and NHR-80.[80] ω-3 and ω-6 polyunsaturated fatty acids are transported to distant tissues by LBP-3 and LBP-5, and OEA is transported to the nucleus by LBP-8. Green arrows indicate unconfirmed activation during fasting conditions. Dotted lines illustrate likely pathways that have not been directly tested (intermediate steps are likely). III. Lysosomal calcium activates lysosomal biogenesis and autophagy. Starvation triggers calcium release from the lysosome through the MCOLN1 channel. Calcium then activates the phosphatase PPP3/calcineurin, which dephosphorylates TFEB promoting its translocation to the nucleus where it transcribes genes involved in lysosomal biogenesis and autophagy.[116] LAL, lysosomal acid lipases.

AKT-MTOR pathway, and induce phosphorylation of BCL2, thereby promoting its dissociation from BECN1/Beclin 1 which results in the activation of autophagy.[114] These observations, in addition to ω-3 and ω-6 PUFAs activating autophagy in human cells in culture,[112] suggest that the role of lysosome-derived lipid metabolites in organismal homeostasis may be conserved all the way up to humans.

The lysosome is the second largest store of calcium in the cell. The presence of calcium microdomains on the surface of the lysosome suggests a role for calcium in relaying messages from this organelle.[115] During starvation, TFEB becomes dephosphorylated enabling it to enter the nucleus and transcribe its target genes (Fig. 2). High-content short interfering RNA screening based on cytoplasm-to-nucleus shuttling of TFEB during starvation revealed that the calcium/calmodulin-dependent phosphatase PPP3/calcineurin is responsible for dephosphorylating TFEB, an essential requirement for its translocation to the nucleus.[116] Starvation of HeLa cells induces the release of calcium from the lysosome through the MCOLN1 channel without affecting endoplasmic reticulum calcium levels. Inhibition of MCOLN1 impairs the nuclear translocation of TFEB, and the induction of autophagy.[116] Thus, lysosomal calcium signaling controls autophagy through PPP3/calcineurin-mediated activation of TFEB.

Beyond its classic role in protein quality control and selective clearance lies a regulatory role for CMA where the upregulation of this autophagy mechanism allows for adaptation to stress and the activation of homeostatic transcriptional programs.[117] Cuervo et al. showed that during nutrient deprivation, the increase in transcription factor NFKB (nuclear factor of kappa light polypeptide gene enhancer in B-cells) activity is dependent on lysosomal degradation of NFKBIA/IκB (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, α).[118] Thus, lysosomal proteolysis is required for the regulation of genes involved in inflammation, cell proliferation and cell death in conditions of nutritional stress.

Future directions

We have described the role of the lysosome in: 1) nutrient sensing, 2) processing of energy-dense nutrients, and 3) the emission of signals that distally control or modulate energy homeostasis (Fig. 3). The critical role of the lysosome in ensuring organismal homeostasis is made evident by the striking

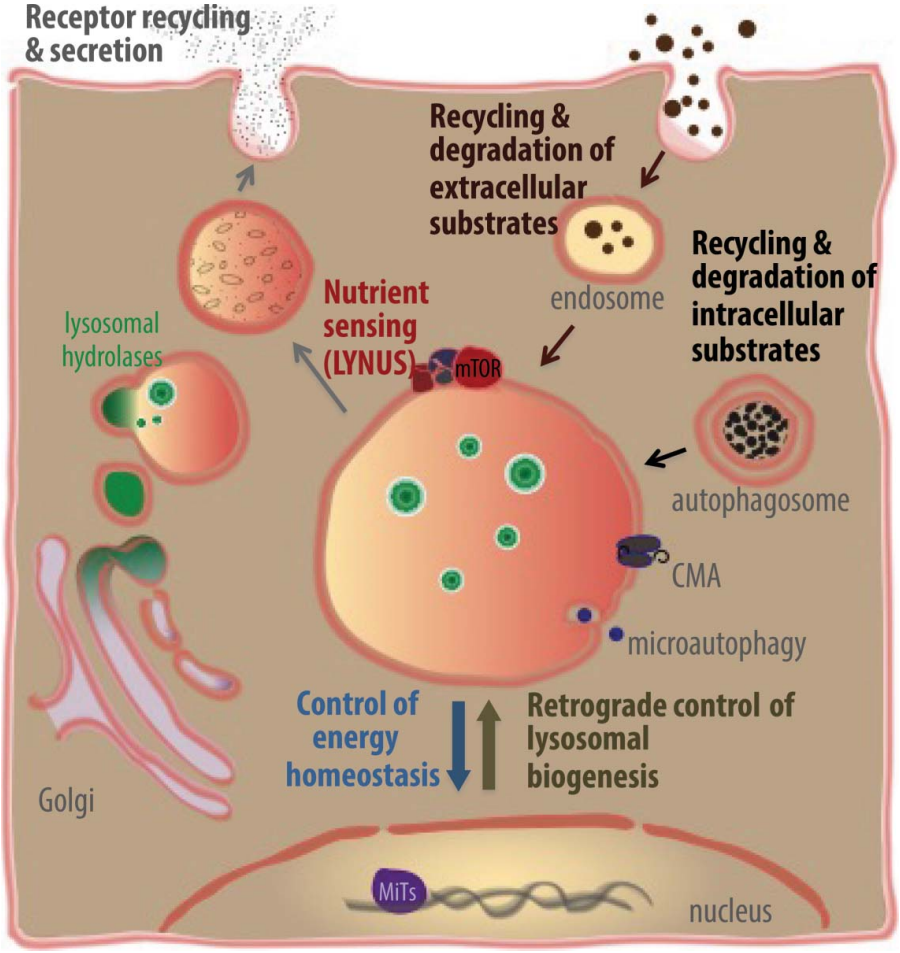

Figure 3. The lysosome is a nutrient sensing, processing and signaling center. The lysosome is the only organelle that receives nutrients and nutritional information from the cell (autophagy) and from the environment (endocytosis). Some of the roles of the lysosome in nutrient homeostasis include: I) sensing of nutrients and growth factors by the Lysosome Nutrient Sensing (LYNUS) machinery, II) digestion and recycling of circulating nutrients (i.e., cholesterol), growth factors (i.e., GH1 [growth hormone 1]), and nutrient regulators (i.e., perilipins); III) digestion and recycling of intracellular macromolecules and organelles; IV) recycling of growth factors, growth factor receptors (i.e., for GH1 and insulin), and nutrient receptors (i.e., LDLR/LDL receptor), V) coordination of responses to fluctuations in nutrient availability by releasing signaling molecules that activate homeostatic responses (i.e., cholesterol biosynthesis or activation of autophagy) locally and in distant cells and tissues; VI) controlling its own biogenesis, and VII) storage. All together, these functions provide building blocks and energy units to promote growth and reproduction, but most importantly the lysosome integrates nutritional information from the cell and the environment so that growth and reproduction are only promoted when conditions are favorable to do so.

conservation of its regulation and function. Comprehensive understanding of the role of the lysosome in essential biological functions, such as growth and reproduction, and in human disease requires broad approaches. Genomics, transcriptomics, proteomics, and lipidomics of patient-derived samples may reveal variations in sequence, expression, and activity of lysosomal proteins as well as its derived metabolites. These variants may either have predisposing, protective, or no effect on disease onset or progression. Therefore, functional genomics approaches in simpler model systems may help elucidate how these variants, and others too disruptive to be found in human populations, affect how the lysosome senses, processes, and relays information, and ultimately defines organismal homeostasis.

A few examples of important advances would be: 1) the discovery of protein complexes specialized in sensing other amino acids, nutrients other than amino acids, growth factors, or stress signals. The existence of complexes sensing specific amino acids, and the fact that these complexes share most but not all of their components supports the hypothesis that different lysosomal sensors could assess nutrients like fats or carbohydrates, as well as growth factors, or stress signals, so as to coordinate growth with the physiological status of the organism and the environment; 2) determining how lysosome-generated signals influence the function of other nutrient sensors, organelles, or distant cells; 3) defining the role of the lysosome in the flow of energy/nutrients to growth or reproduction. Lysosomes are directly involved in integrating nutrients and nutritional information to decide when to promote growth. Lysosomes also control reproduction through the mobilization of yolk particles. Thus, lysosomes are uniquely positioned to play a role in deciding soma vs. germline nutrient allocation; 4) assessing to which extent and how lysosomal signaling and function contribute to health span. We predict the lysosome will have roles in health span beyond being the digestive companion of autophagy.

We expect the body of knowledge on lysosomal structure, function, and regulation generated by the combination of 'omics' with traditional and emerging genetics and cell biological approaches will provide us with the ability to target lysosomal function to improve human health.

Abbreviations

AMPK	AMP-activated protein kinase
BORCS6	BLOC-1 related complex subunit 6
CMA	chaperone-mediated autophagy
GAPDH	glyceraldehyde 3-phosphate dehydrogenase
GATOR	GTPase-activating protein toward Rag GTPases
GEF	guanine nucleotide exchange factor
LDL	low density lipoprotein
MCOLN	mucolipin 1
MITF	microphthalmia-associated transcription factor
MiTs	MITF, TFE3 and TFEB transcription factors
MTOR	mechanistic target of rapamycin (serine/threonine kinase)
NHR	nuclear hormone receptor
NPC1	Niemann-Pick disease, type C1
OEA	oleoylethanolamide
PUFA	polyunsaturated fatty acid
RHEB	Ras homolog enriched in brain
SCAP	SREBP chaperone
SREBF	sterol regulatory element binding transcription factor
TFEB	transcription factor EB
TPCN	two pore segment channel
TSC	tuberous sclerosis complex
V-ATPase	vacuolar-type H^+ adenosine triphosphatase

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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