Defective collagen proteostasis and matrix formation in the pathogenesis of lysosomal storage disorders

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Abstract

The lysosome is a catabolic organelle devoted to the degradation of cellular components, such as protein complexes and whole or portion of organelles that reach the lysosomes through (macro)autophagy. The lysosomes also function as signaling organelles by controlling the activity of key metabolic kinases, such as the mechanistic target of Rapamycin complex 1 (mTORC1). Lysosome dysfunction has dramatic consequences on cellular homeostasis and cause lysosomal storage disorders (LSDs). Here we review the recently proposed mechanisms by which impairment of lysosome/autophagy pathway affects extracellular matrix formation and skeletal development and growth. In particular, we will highlight the role of autophagy as a collagen quality control pathway in collagen-producing cells. An impairment of autophagy, such as the one observed in LSDs, leads to a collagen proteostatic defects and can explain, at least in part, the skeletal phenotypes characterizing patients with lysosomal storage disorders.

Introduction

Lysosomes were identified in 1955 by Christian De Duve [1] who received the Nobel Prize in 1974 with Albert Claude, and George Palade "for their discoveries concerning the structural and functional organization of the cell." The discovery of the lysosome opened a new era in cellular physiology and allowed the identification of approximately 70 diseases, known as lysosomal storage disorders (LSDs), that result from mutations in genes encoding for lysosomal enzymes.

Several exciting discoveries made in the past 10 years have led to a broader understanding of lysosomal biology and rehabilitated this organelle from a merely degradative bag to an important player in the regulation of multiple cellular functions, such as response to nutrients, lipid metabolism, immune response, cell motility and protein secretion. This increasing knowledge is also giving us the opportunity to study the cellular consequences of lysosomal dysfunction and hence to understand the pathophysiology of lysosomal storage disorders.

In this review article we will describe the role of lysosomes, not only as degradative organelles, but also as cellular signaling hubs that coordinate different pathways in response to both intra- and extracellular cues. We will focus on the role of lysosomes in controlling proteostasis of type I and type II collagens, the major components of extracellular matrix in skeletal tissues: bones and cartilages, respectively. The contribution of these novel lysosomal functions will be discussed in the context of LSDs, multi-organ diseases in which the skeleton represents one of the most affected tissues and for which current therapies are still ineffective.

The lysosome

Lysosomes are organelles devoted to the degradation of exhausted intra- and extra-cellular material. This organelle has an exceptionally broad and efficient digestive capacity due to the large amount of hydrolytic enzymes that reside within its lumen. Lysosomal hydrolases can be classified into major groups according to substrate's specificity: nucleases, proteases, glycosidases, lipases, phosphatases, sulfatases and phospholipases [2]. For maximum activity, lysosomal hydrolases require an acidic environment (pH less than 5) that is generated by transmembrane ion channels and pumps, such as the V-ATPase proton pump. Lysosomal degradation guarantees the turnover of cellular components and prevents the accumulation of exhausted materials

within cells. The presence of transmembrane lysosomal transporters allows to recycle the products generated from the degradation back to the cytoplasm to be used as building blocks for the biosynthesis of new cellular components or as a direct source of energy. Consistently, lysosomal activity is enhanced during nutrient starvation in order to sustain cell survival in the absence of external nutrient sources.

Lysosome biogenesis is a coordinated process that requires the activity of the microphtalmia transcription factor family (MiTF), particularly TFEB and TFE3, which bind to the promoters of several lysosomal genes inducing their expression [3]. These transcription factors also promote the expression of genes involved in lysosome biogenesis, such as the mannose 6-phospate receptors, which transport newly synthesized lysosomal enzymes from Golgi to lysosomes. The activity of TFEB and TFE3 is regulated according to cellular needs by multiple kinases, in particular the mechanistic target of rapamycin complex 1 (mTORC1) and by the phosphatase calcineurin that act on multiple serine residues [4][5][6][7]. When phosphorylated, TFEB and TFE3 are retained in the cytoplasm and inhibited. Several stress signals, such as nutrient deprivation, proteotoxicity, and lysosomal damage have been reported to promote TFEB/TFE3 dephosporylation, nuclear translocation and activation, leading to an increase in the number and activity of lysosomes [8]. In addition to TFEB and TFE3, a growing number of transcriptional regulators have been identified as lysosomal biogenesis regulators in response to nutrient fluctuations, such as the transcriptional regulators BRD4 and ZKSCAN3[9][10].

Recent data showed that the lysosome functions as a platform for the activity of different kinases, including AMPK, AKT and mTORC1, defining the lysosome as a signaling hub that coordinates several homeostatic signaling pathways in response to both intra- and extracellular cues [11][12]. To date the best characterized example of cross talk between lysosomes and kinases is represented by the lysosomal regulation of mTORC1 [13]. mTORC1 is potently activated by nutrients (amino acids, glucose, lipids) and growth factors, and conversely is inhibited by starvation [14]. The activation/inactivation of mTORC1 in response to nutrient availability occurs on the lysosome and is regulated by a growing number of lysosomal membrane-associated and transmembrane proteins [15][16]. Notably, the lysosome does not only function as a scaffolding organelle, but also directly engages in the nutrient sensing process. In fact, the proton pumping V-ATPase and the transmembrane protein SLC38A9 sense luminal levels of nutrients and convey

this information to the Ragulator/Rags complex on the lysosome [17][18][19][20]. In addition, the delivery of autophagy cargo to the lysosome promotes mTORC1 reactivation during starvation [21], further underscoring the role of lysosomal catabolism as a regulator of mTORC1 signaling. The regulation of mTORC1 signaling by the lysosome also occurs through a transcriptional mechanism mediated by TFEB and TFE3 transcription factors, which are activated in response to lysosomal stress. Once in the nucleus they strongly enhance the expression of *RragD* and *RragC* genes, encoding for RAGD and C, respectively, which in turn promote the association of mTORC1 to lysosomes [22].

The lysosome is the terminal station for the degradation of different cargoes, whose relative abundance reflects the metabolic and environmental conditions of the cell, and thus "*a posteriori*" it is not difficult to understand why cells evolved a machinery that senses lysosomal contents and conveys this information to hubs involved in the regulation of cellular metabolism. To date however the physiological relevance of the lysosome as signaling organelle remains to be elucidated. These studies are complicated by the presence of feedback mechanisms and cell specific regulation of metabolic pathways. However, addressing this question in the future will be of critical importance in light of the growing list of diseases in which lysosomal dysfunction has been implicated.

Substrate delivery to lysosomes: the macroautophagy pathway

Substrates are delivered to the lysosome through vesicular pathways that rely on membrane fusion events. Plasma membrane proteins and extracellular materials are delivered to lysosomes through endocytosis (for review see [23]). Intracellular substrates instead reach the lysosomes via autophagy. Currently, three main forms of autophagy have been described: macro-autophagy [24], micro-autophagy and chaperon mediated autophagy [25]. During macro-autophagy, herein after referred as autophagy, specific substrates are sequestered within vesicular structures known as autophagosomes and subsequently delivered to the lysosome upon autophagosome-lysosome fusion [26]. Autophagy substrates are recognized via receptors that simultaneously bind cargoes destined for degradation and the LC3s/GABARAPs autophagosome-associated membrane proteins. A classical example is represented by the autophagy receptor P62/SQSTM1, which possesses a ubiquitin-binding domain for the recognition of ubiquitinilated proteins and an LC3-interaction sequence (LIR) that

binds the LC3 protein associated to the inner membrane of a nascent autophagosome [27]. Once fully sealed, the autophagic vesicles that contain cytosolic material move along microtubules towards the cell center where they fuse with the lysosome [28] [29]. Upon fusion, both cargoes and autophagic membranes are digested by the lysosomal hydrolases.

Lysosomal membrane fusion with donor membrane organelles is a critical step during both endocytic and autophagic pathways. Indeed, a growing list of pathological conditions, such as aging and obesity, are often characterized by inefficient lysosomal fusion, which leads to a generalized impairment of the lysosomal-mediated recycling processes [30][31][32].

The autophagic pathway is triggered by several forms of cellular stress, including hypoxia, oxidative stress, DNA damage, protein aggregates formation, damaged organelles or invading intracellular pathogens. The most potent autophagy inducer is nutrient starvation. The cell reacts to the lack of nutrients by activating a bulk catabolism of intracellular components, allowing the cell to generate significant energy source during periods of nutrient scarcity [33].

Autophagy is strongly inhibited by the mTORC1 kinase, through both transcriptional and post-translational mechanisms. mTORC1 inhibits AV biogenesis by phosphorylating the autophagy initiation ULK1 kinase complex [34] that in turn phosphorylates multiple proteins involved in autophagosome biogenesis [35], such as Beclin1 [36]. Emerging data suggest that mTORC1 also controls autophagosome maturation (e.g. fusion with lysosomes) by direct phosphorylation of fusion machinery components, such as UVRAG [37] and ATG14 [38]. Furthermore, mTORC1 has been shown to suppress transcription of autophagy genes, as well as of lysosomal genes, by inhibiting TFEB and TFE3 activity [7][6][4][39]. Hence, mTORC1 controls both lysosome and autophagosome biogenesis and their cooperative function.

In addition to mTORC1, additional kinases (such as AMPK, JNK, EGFR and AKT)[40][41][42] and phosphatases (such as Jumpy, MTMR3, Calcineurin and PP2A)[43][44][45] have been shown to regulate autophagy and lysosome biogenesis through transcriptional, post transcriptional and epigenetic mechanisms unveiling an extremely highly dynamic regulation of the main cellular catabolic compartments.

Lysosome/autophagy pathway in the regulation of extracellular matrix and collagen proteostasis

The extracellular matrix (ECM) plays a fundamental role in maintaining tissue architecture and contributes to the development and function of tissues by modulating the activity of endocrine and paracrine signaling molecules [46][47]. As result, both physiological and pathological changes in the composition of the ECM have been shown to alter autophagy activity. For example autophagy is activated during anoikis and promotes epithelial cell survival [48]. Currently, a growing list of molecules, representing a diverse repertoire of matrix constituents (decorin, collagen VI, laminin a2, endostatin, endorepellin, and kringle V), modulate autophagy either positively or negatively (reviewed in [49]). This regulation seems to be physiologically relevant since mice lacking Collagen VI or decorin expression, a secreted proteoglycan[50], have impaired autophagy responses in vivo [51][52][53]. Autophagy, in turn, may control the composition of the extracellular matrix by modulating either directly or indirectly cellular secretion[54].

Bones and cartilages, the two tissues composing the skeleton, are the most ECM enriched tissues of the body [55][56]. The major components of their ECM are collagens and proteoglycans[56][55]. Proteoglycans are composed of a core protein decorated with sulfated glycosaminoglycan (GAG) chains, namely chondroitin, dermatan, heparan and keratan sulfate [57]. Collagens are the most abundant proteins in the animal kingdom [58]. In particular, type I and type II collagens are the most abundant proteins of bone and cartilage, respectively. Collagens are composed of three single polypeptide alpha chains which form triple helices; type II collagen is made of three identical chains while type I collagen is made of two alpha1 and one alpha2 polypeptide [58]. Mutations in genes encoding for components of the ECM or for proteins involved in ECM folding and/or secretion are in most of the cases associated to severe skeletal disorders [59][60][61]**.** In the ER, individual procollagen chains are produced, and, with the assistance of various chaperones, these chains are folded and stabilized into triple helices. The association with the Heat Shock protein 47 (HSP47) chaperone is required to maintain the triple helix state which is energetically unfavorable, avoiding the formation of disordered aggregate structures [62]. Once properly assembled, native procollagen (PC) molecules are packaged into COPII coated carriers at ER exit sites (ERES)[63]. However, due to their large size (300nm long), the triple helices cannot fit into regular COPII carriers (60 nm

diameter), and their packaging must be aided by additional adaptor proteins such as TANGO1, CTAGE5 and Sedlin1[64][65]. Thus, given the complexity of folding and secretion it is not surprising that approximately 10-30% of newly synthesized molecules fail to be secreted because of folding and secretion defects, and are degraded [66][67]. This fraction increases significantly in case of mutations in collagen genes or in critical chaperones. Collagen alpha chains harbouring mutations that interfere with initial steps of folding are retro-translocated into the cytosol and degraded by the proteasome through the classical ERAD pathway [68]. Conversely, PC molecules containing mutations affecting triple helix conformation are precluded from retrotranslocation and are likely to be degraded by the lysosomes [68]. For example, cells lacking HSP47, that is mutated in a subset of Osteogenesis Imperfecta patients, showed accumulation of misfolded type I collagen in the ER[69]. This accumulation is counteracted by autophagy and not by the ERAD pathway [68]. Consistently, inhibition of autophagy in HSP47 null fibroblasts further exacerbates the ER storage phenotype and triggers apoptosis [68]. Conversely, treating cells with rapamycin, a mTORC1 inhibitor, enhanced the clearance of procollagen aggregates from the ER [68].

Cartilage chondrocytes secrete a massive amount of type II collagen, particularly during post-natal bone elongation. Deletion of the essential autophagy gene *ATG7* in these cells causes a progressive accumulation of aggregate-like type II procollagen molecules within the ER and, as a consequence, a defective secretion of type II collagen in the ECM [70]. Notably, this accumulation also occurs in absence of genetic mutations, suggesting that autophagy has a physiologically relevant role in collagen quality control.

The mechanism by which autophagy supports collagen secretion is currently unknown. Neither lysosomes nor autophagosomes containing procollagen molecules appear to fuse directly with the plasma membrane, arguing against a direct role of the lysosome autophagy pathway in collagen secretion [70]. *In vivo,* chondrocytes in growth plates, which lack autophagy, progressively show formation of aggregate-like collagen structures in which HSP47 appears sequestered [70]. These data suggest that the clearance of spontaneously occurring misfolded collagen molecules by autophagy maintains and efficient ER folding and secretion.

In addition, the lysosome may regulate collagen production via mTORC1. mTORC1 promotes anabolic processes, such as protein synthesis through the phosphorylation of p70S6 Kinase 1 (S6K1) and eIF4E Binding Protein (4EBP). S6K1 phosphorylates and

activates several substrates resulting in a global increase in mRNA biogenesis, cap-dependent translation and elongation, and translation of ribosomal proteins. Concomitantly, phosphorylation of 4E-BP1 prevents its binding to eIF4E, enabling eIF4E to promote cap-dependent translation [71]. Notably, the synthesis of collagens, main components of extracellular matrices, appears to be particularly sensitive to the activity of mTORC1 [72][73], suggesting that lysosomal function may indirectly regulate the composition and quality of the extracellular matrix via mTORC1 signaling [74] (see also below).

Furthermore, the inhibition of autophagy and of lysosome function in chondrocytes decreases collagen transcription, as a probable compensatory mechanism to slow down the folding rate and to counteract accumulation of collagen intermediates within the ER (Cinque, Bartolomeo and Settembre, unpublished observations)[75]. Currently, the transcriptional circuitry that regulates collagen levels in response to the status of the lysosome/autophagy pathway is currently unknown. Overall, these data suggest that the lysosome autophagy pathway is essential to maintain collagen proteostasis (Figure 1a).

ER-phagy: regulation of Endoplasmic Reticulum (ER) turnover and function via autophagy

The lysosome autophagy pathway may also influence the composition and the amount of extracellular matrix by regulating ER function. Indeed, secreted proteins are synthesized within the ER. The lysosome autophagy pathway contributes to the maintenance of ER function by mediating its turnover, through a process known as ER-phagy [76]. During ER-phagy a discrete portion of the ER is sequestered by nascent autophagosomes and delivered to the lysosome for degradation. To date, four different ER transmembrane proteins have been identified as ER-phagy receptors that mediate turnover of ER subdomains in response to specific cellular conditions in mammals [77][78][79][80]. In particular, FAM134B and reticulon 3 (RTN3) mediate the degradation of ER sheets and tubules, respectively, in response to nutrient starvation [77][78]. The ER protein SEC62 functions as a receptor for the “ER-phagy mediated recovery from ER stresses” (recovER-phagy) [80]. Pathological or physiological conditions characterized by high biosynthetic demands lead to a transient but dramatic expansion of the ER volume and content; the subsequent recovery to basal conditions is mediated by SEC62-mediated recovER-phagy. More recently, an ER-stress induced ER-phagy was shown to be triggered by CCPG1, a

single pass ER membrane protein that is transcriptionally upregulated in response to ER stressors and mediates the autophagic depletion of peripheral ER [79]. Notably, studies in mice show that CCPG1 protects against ER luminal protein aggregation suggesting a role of ER-phagy as an ER quality control mechanism. These data suggest that ER-phagy is also a quality control mechanism by which ER proteostasis is maintained. It is well known that the folding process within the ER is an error- prone mechanism [81]. In fact, the majority of misfolded polypeptides are translocated across the ER membrane and degraded in the cytosol by the proteasome via the classical ER associated degradation (ERAD) pathway [82]. However, in the last years a growing number of ER substrates, including collagens, were shown to be resistant to proteasome degradation but sensitive to lysosomal degradation[83][68][70][84]. One possibility is that ER-phagy mechanisms operate to deliver ERAD-resistant clients to lysosomes. However, the mechanism by which the autophagic machinery operating in the cytosol could selectively sequester ER subdomains that contain proteasome-resistant misfolded clients is still unknown.

Collagen, mTORC1 and ER defects in the pathogenesis of lysosomal storage disorders

Cargo degradation in lysosomes is a stepwise process and the impairment of a single enzymatic reaction leads to the accumulation of intermediate substrates (the so called storage) within the lysosomes [85]. This condition characterizes patients affected by LSDs, a group of over 70 inherited metabolic disorders caused by loss of function mutations in genes encoding for lysosomal enzymes or for regulators of lysosomal biogenesis [85]. LSD patients present progressive and multi-organ disease manifestations. Main affected tissues include brain and skeleton, for which current enzymatic replacement therapies are still largely ineffective [86][87]. The onset and the severity of disease manifestation depend on the enzymatic defect, the nature of storage substrates and cell type affected. The cellular pathogenesis of the diseases is complex, since a progressive accumulation of primary substrates within lysosomes induces a generalized lysosomal dysfunction, which in turn leads to the accumulation of a variety of secondary storage products that eventually contribute to disease manifestation [88].

To date, many different pathogenic mechanisms have been proposed to trigger cellular dysfunction and death in LSDs. The discovery of new lysosome roles (such as regulation of cell motility, signaling, phagocytosis, immune responses, inter-organellar crosstalk via

contact sites, ion homeostasis, etc) [89][3] [90] [91] will indubitably extend the list of the mechanisms that contribute to LSD disease pathology. Here the possible role of mTORC1 signaling and of ER/collagen dysfunction in the pathogenesis of bone and cartilage phenotype in LSDs will be discussed.

Cells from LSD models display defective autophagy, mostly at the level of autophagosome-lysosome fusion and defective lysosome reformation after fusion with autophagosomes [92][21]. In chondrocytes isolated from patients and murine models of a subfamily of LSD, mucopolysaccharidoses (MPS), we have recently demonstrated that observed lysosomal dysfunction leads to an increase in the association of mTORC1 to lysosomal membranes resulting in an increased kinase activity [93]. Similar data were obtained in chondrocytes where lysosomal function was inhibited pharmacologically [94]. The increase in mTORC1 activity may itself contribute to the cellular LSD phenotype in multiple ways. mTORC1 inhibited autophagosome-lysosome fusion in MPS chondrocytes mediated, in part, by the UV radiation resistance-associated gene protein (UVRAG) (Bartolomeo et al 2017) [37]. mTORC1 phosphorylates UVRAG at serine 497, and enhances its affinity for RUN domain Beclin 1-interacting and cysteine rich containing protein (RUBICON), which antagonizes UVRAG activity [37]. The inhibition of UVRAG by Rubicon may inhibit autophagosome-lysosome fusion through two independent mechanism: 1) as part of the VPS34 complex, UVRAG promotes the production of phosphatidylinositol 3-phosphate (PI3P) on endosomes and lysosomes membranes [95][96]. PI3P is required to attract several proteins involved in membrane tethering and fusion, which harbor a PI3P binding domain. 2) UVRAG interacts with and promotes the activity of the HOPS complex, which mediates the tethering of lysosomal membranes with endosomes and autophagosomes [97][98]. The inhibition of mTORC1 or the forced overexpression of UVRAG in MPS chondrocytes significantly rescued autophagosome fusion with lysosomes and autophagy substrate degradation [93]. Notably, enhanced mTORC1 signaling is not a general feature of LSD cells, such as in Pompe disease, mTORC1 activity was found to be inhibited, suggesting that storage material may be sensed by mTORC1 differently [99]. The mechanism by which mTORC1 signaling is enhanced in LSD chondrocytes is still unknown. Intriguingly, an aberrant accumulation of cholesterol in lysosomes was recently shown to activate mTORC1 signaling via an SLC38A9–Niemann-Pick C1 signaling complex [20]. Cholesterol has been reported as a secondary storage product that accumulates in cells with lysosomal

dysfunction and impairs the activity of SNARE proteins devoted to lysosomal fusion with autophagosomes [100]. These observations suggest that cholesterol accumulation in lysosomes enhances mTORC1 activity and in turn inhibits lysosome fusion with autophagosomes in LSD. There are many functional consequences of impaired autophagy in LSD cells. For example, accumulation of poly-ubiquitinated proteins and of dysfunctional mitochondria, known autophagy substrates, has been observed in multiple LSD cell types and are considered important contributors to cellular dysfunction [92]. Secretory cells, such as chondrocytes and osteoblasts, may also have additional problems. In particular, MPS chondrocytes show ER distention, accumulation of type II procollagen in the ER and a defective ER-to Golgi trafficking [93]. These defects appear to be physiologically relevant since collagen contents were reduced in cartilages isolated from MPS mice compared to wild type [93][101][102]. Why the secretion efficiency of procollagen molecules, leading to accumulation in the ER, is hampered in LSD chondrocytes is still unknown. One possibility is that lysosomal and autophagy dysfunctions inhibit ER-phagy and in turn ER folding and secretion capacity leading to accumulate abundant and/or difficult to fold cargoes, such as procollagens. Indeed, earlier studies have shown an ER calcium homeostasis dysfunction in different LSDs, particularly those characterized by lipid accumulation, suggesting a generalized ER dysfunction in LSDs. Whether the ER dysfunction in LSD is due to a defective ER-phagy is still unexplored. Another possibility is that a yet to be discovered selective recognition of misfolded and ERAD-resistant ER clients by autophagy is impaired in LSD cells. A defect in autophagy may also induce a transcriptional downregulation of collagen genes [101] [75] probably as a feedback mechanism to limit the accumulation of newly synthesized procollagens in cells with defective quality control mechanisms (figure 1b).

In addition to its negative impact on autophagy, enhanced mTORC1 signaling may, in principle, exacerbate the perturbation of proteostasis in the ER of LSD cells. Indeed, mTORC1 promotes protein synthesis and procollagen molecules appear to be particularly sensitive to the activity of mTORC1. Thus, mTORC1 might concomitantly increase collagen synthesis and inhibit its autophagy-mediated quality control in the ER leading to unbalanced ER proteostasis that favors the formation of aggregates within the ER. This scenario may not be limited to procollagen but also involve other aggregate-prone cargoes synthesized within the ER of secretory cells such as osteoblasts and chondrocytes. Unbalanced mTORC1 signaling has been recently associated to the

development of osteoarthritis. The mechanisms by which mTORC1 signaling promotes osteoarthritis seem to be related to the suppression of autophagy pathway [103]. Consistently, mice with chondrocyte specific deletion of autophagy genes develop osteoarthritis [104] and inhibition of mTORC1 signaling protects from the development of osteoarthritis by inducing autophagy [105]. Recent data indicate that members of the FOXO family of transcription factors protect from osteoarthritis by promoting the expression of autophagy genes in chondrocytes [106]. Whether autophagy protects from osteoarthritis by maintaining ER homeostasis and procollagen proteostasis is currently unknown. Notably, osteoarthritis is frequently observed in LSD patients with skeletal involvement, suggesting that similar pathogenetic mechanisms may trigger cartilage erosion in LSD and osteoarthritis patients.

Conclusions

In this review article we have summarized the principal pathways through which lysosome activity can influence the composition of tissue extracellular matrices. Impairment of the lysosome-related processes, as consequences of lysosomal dysfunction, may alter proteostasis of essential components of extracellular matrix and, in turn, contribute to the skeletal phenotypes observed in patients affected by lysosomal storage disorders. This alteration may not only be limited to collagens but also involve other components of the ECM, such as glycosaminoglycans, which controls the activity of growth factors and ligands [107][108][101][109].

Many open questions still remain unanswered. For example it is unknown the transcriptional circuitry that inhibits the transcription of collagens and other ECM components in response to lysosomal dysfunction. Also, it is still largely unexplored whether a modulation of lysosome biogenesis and autophagy during development contributes to tissue formation and organismal growth. Indeed, a selective remodeling of cytosolic composition via autophagy may shape cell identities and functions during tissue development and growth. Finally, it will be also important to investigate the physiological role of the lysosome as signaling organelle, and its role in more common diseases such as cancer.

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References:

[1] F. Appelmans, R. Wattiaux, C. De Duve, Tissue fractionation studies. 5. The association of acid phosphatase with a special class of cytoplasmic granules in rat liver, Biochem. J. 59 (1955) 438–445.

[2] J.P. Luzio, P.R. Pryor, N.A. Bright, Lysosomes: fusion and function, Nat. Rev. Mol. Cell Biol. 8 (2007) 622–632. doi:10.1038/nrm2217.

[3] C. Settembre, A. Fraldi, D.L. Medina, A. Ballabio, Signals from the lysosome: a control centre for cellular clearance and energy metabolism, Nat. Rev. Mol. Cell Biol. 14 (2013) 283–296. doi:10.1038/nrm3565.

[4] C. Settembre, R. Zoncu, D.L. Medina, F. Vetrini, S. Erdin, S. Erdin, T. Huynh, M. Ferron, G. Karsenty, M.C. Vellard, V. Facchinetti, D.M. Sabatini, A. Ballabio, A lysosome-to-nucleus signalling mechanism senses and regulates the lysosome via mTOR and TFEB, EMBO J. 31 (2012) 1095–1108. doi:10.1038/emboj.2012.32.

[5] J.A. Martina, H.I. Diab, L. Lishu, L. Jeong-A, S. Patange, N. Raben, R. Puertollano, The nutrient-responsive transcription factor TFE3 promotes autophagy, lysosomal biogenesis, and clearance of cellular debris, Sci. Signal. 7 (2014) ra9. doi:10.1126/scisignal.2004754.

[6] A. Roczniak-Ferguson, C.S. Petit, F. Froehlich, S. Qian, J. Ky, B. Angarola, T.C. Walther, S.M. Ferguson, The transcription factor TFEB links mTORC1 signaling to transcriptional control of lysosome homeostasis, Sci. Signal. 5 (2012) ra42. doi:10.1126/scisignal.2002790.

[7] S. Vega-Rubin-de-Celis, S. Peña-Llopis, M. Konda, J. Brugarolas, Multistep regulation of TFEB by MTORC1, Autophagy. 13 (2017) 464–472. doi:10.1080/15548627.2016.1271514.

[8] G. Napolitano, A. Ballabio, TFEB at a glance, J. Cell Sci. 129 (2016) 2475–2481. doi:10.1242/jcs.146365.

[9] J.-I. Sakamaki, S. Wilkinson, M. Hahn, N. Tasdemir, J. O'Prey, W. Clark, A. Hedley, C. Nixon, J.S. Long, M. New, T. Van Acker, S.A. Tooze, S.W. Lowe, I. Dikic, K.M. Ryan, Bromodomain Protein BRD4 Is a Transcriptional Repressor of Autophagy and Lysosomal Function, Mol. Cell. 66 (2017) 517-532.e9. doi:10.1016/j.molcel.2017.04.027.

[10] S. Chauhan, J.G. Goodwin, S. Chauhan, G. Manyam, J. Wang, A.M. Kamat, D.D. Boyd, ZKSCAN3 is a master transcriptional repressor of autophagy, Mol. Cell. 50 (2013) 16–28. doi:10.1016/j.molcel.2013.01.024.

[11] C.-S. Zhang, B. Jiang, M. Li, M. Zhu, Y. Peng, Y.-L. Zhang, Y.-Q. Wu, T.Y. Li, Y. Liang, Z. Lu, G. Lian, Q. Liu, H. Guo, Z. Yin, Z. Ye, J. Han, J.-W. Wu, H. Yin, S.-Y. Lin, S.-C. Lin, The Lysosomal v-ATPase-Ragulator Complex Is a Common Activator for AMPK and mTORC1, Acting as a Switch between Catabolism and Anabolism, Cell Metab. 20 (2014) 526–540. doi:10.1016/j.cmet.2014.06.014.

[12] E. Arias, H. Koga, A. Diaz, E. Mocholi, B. Patel, A.M. Cuervo, Lysosomal mTORC2/PHLPP1/Akt Regulate Chaperone-Mediated Autophagy, Mol. Cell. 59 (2015) 270–284. doi:10.1016/j.molcel.2015.05.030.

[13] L. Bar-Peled, D.M. Sabatini, SnapShot: mTORC1 signaling at the lysosomal surface, Cell. 151 (2012) 1390-1390.e1. doi:10.1016/j.cell.2012.11.038.

[14] R.A. Saxton, D.M. Sabatini, mTOR Signaling in Growth, Metabolism, and Disease, Cell. 168 (2017) 960–976. doi:10.1016/j.cell.2017.02.004.

[15] C.-Y. Lim, R. Zoncu, The lysosome as a command-and-control center for cellular metabolism, J. Cell Biol. 214 (2016) 653–664. doi:10.1083/jcb.201607005.

[16] R.M. Perera, R. Zoncu, The Lysosome as a Regulatory Hub, Annu. Rev. Cell Dev. Biol. 32 (2016) 223–253. doi:10.1146/annurev-cellbio-111315-125125.

[17] R. Zoncu, L. Bar-Peled, A. Efeyan, S. Wang, Y. Sancak, D.M. Sabatini, mTORC1 senses lysosomal amino acids through an inside-out mechanism that requires the vacuolar H(+)-ATPase, Science. 334 (2011) 678–683. doi:10.1126/science.1207056.

[18] M. Rebsamen, L. Pochini, T. Stasyk, M.E.G. de Araújo, M. Galluccio, R.K. Kandasamy, B. Snijder, A. Fauster, E.L. Rudashevskaya, M. Bruckner, S. Scorzoni, P.A. Filipek, K.V.M. Huber, J.W. Bigenzahn, L.X. Heinz, C. Kraft, K.L. Bennett, C. Indiveri, L.A. Huber, G. Superti-Furga, SLC38A9 is a component of the lysosomal amino acid sensing machinery that controls mTORC1, Nature. 519 (2015) 477–481. doi:10.1038/nature14107.

[19] S. Wang, Z.-Y. Tsun, R.L. Wolfson, K. Shen, G.A. Wyant, M.E. Plovanich, E.D. Yuan, T.D. Jones, L. Chantranupong, W. Comb, T. Wang, L. Bar-Peled, R. Zoncu, C. Straub, C. Kim, J. Park, B.L. Sabatini, D.M. Sabatini, Metabolism. Lysosomal amino acid

transporter SLC38A9 signals arginine sufficiency to mTORC1, Science. 347 (2015) 188–194. doi:10.1126/science.1257132.

[20] B.M. Castellano, A.M. Thelen, O. Moldavski, M. Feltes, R.E.N. van der Welle, L. Mydock-McGrane, X. Jiang, R.J. van Eijkeren, O.B. Davis, S.M. Louie, R.M. Perera, D.F. Covey, D.K. Nomura, D.S. Ory, R. Zoncu, Lysosomal cholesterol activates mTORC1 via an SLC38A9-Niemann-Pick C1 signaling complex, Science. 355 (2017) 1306–1311. doi:10.1126/science.aag1417.

[21] L. Yu, C.K. McPhee, L. Zheng, G.A. Mardones, Y. Rong, J. Peng, N. Mi, Y. Zhao, Z. Liu, F. Wan, D.W. Hailey, V. Oorschot, J. Klumperman, E.H. Baehrecke, M.J. Lenardo, Termination of autophagy and reformation of lysosomes regulated by mTOR, Nature. 465 (2010) 942–946. doi:10.1038/nature09076.

[22] C. Di Malta, D. Siciliano, A. Calcagni, J. Monfregola, S. Punzi, N. Pastore, A.N. Eastes, O. Davis, R. De Cegli, A. Zampelli, L.G. Di Giovannantonio, E. Nusco, N. Platt, A. Guida, M.H. Ogmundsdottir, L. Lanfrancone, R.M. Perera, R. Zoncu, P.G. Pelicci, C. Settembre, A. Ballabio, Transcriptional activation of RagD GTPase controls mTORC1 and promotes cancer growth, Science. 356 (2017) 1188–1192. doi:10.1126/science.aag2553.

[23] G.J. Doherty, H.T. McMahon, Mechanisms of Endocytosis, Annu. Rev. Biochem. 78 (2009) 857–902. doi:10.1146/annurev.biochem.78.081307.110540.

[24] N. Mizushima, Autophagy in protein and organelle turnover, Cold Spring Harb. Symp. Quant. Biol. 76 (2011) 397–402. doi:10.1101/sqb.2011.76.011023.

[25] K.A. Tekirdag, A.M. Cuervo, Chaperone-mediated autophagy and endosomal microautophagy: joint by a chaperone, J. Biol. Chem. (2017). doi:10.1074/jbc.R117.818237.

[26] J. Kaur, J. Debnath, Autophagy at the crossroads of catabolism and anabolism, Nat. Rev. Mol. Cell Biol. 16 (2015) 461–472. doi:10.1038/nrm4024.

[27] V. Rogov, V. Dötsch, T. Johansen, V. Kirkin, Interactions between Autophagy Receptors and Ubiquitin-like Proteins Form the Molecular Basis for Selective Autophagy, Mol. Cell. 53 (2014) 167–178. doi:10.1016/j.molcel.2013.12.014.

[28] S. Nakamura, T. Yoshimori, New insights into autophagosome-lysosome fusion, J. Cell Sci. 130 (2017) 1209–1216. doi:10.1242/jcs.196352.

[29] R. Jia, C.M. Guardia, J. Pu, Y. Chen, J.S. Bonifacino, BORC coordinates encounter and fusion of lysosomes with autophagosomes, Autophagy. 13 (2017) 1648–1663. doi:10.1080/15548627.2017.1343768.

[30] H. Koga, S. Kaushik, A.M. Cuervo, Altered lipid content inhibits autophagic vesicular fusion, FASEB J. 24 (2010) 3052–3065. doi:10.1096/fj.09-144519.

[31] J.A. Rodriguez-Navarro, S. Kaushik, H. Koga, C. Dall'Armi, G. Shui, M.R. Wenk, G. Di Paolo, A.M. Cuervo, Inhibitory effect of dietary lipids on chaperone-mediated autophagy, Proc. Natl. Acad. Sci. 109 (2012) E705–E714. doi:10.1073/pnas.1113036109.

[32] C. Settembre, A. Ballabio, Lysosome: regulator of lipid degradation pathways, Trends Cell Biol. 24 (2014) 743–750. doi:10.1016/j.tcb.2014.06.006.

[33] N. Mizushima, Autophagy: process and function, Genes Dev. 21 (2007) 2861–2873. doi:10.1101/gad.1599207.

[34] M. Wirth, J. Joachim, S.A. Tooze, Autophagosome formation—The role of ULK1 and Beclin1–PI3KC3 complexes in setting the stage, Semin. Cancer Biol. 23 (2013) 301–309. doi:10.1016/j.semcancer.2013.05.007.

[35] D.F. Egan, M.G.H. Chun, M. Vamos, H. Zou, J. Rong, C.J. Miller, H.J. Lou, D. Raveendra-Panickar, C.-C. Yang, D.J. Sheffler, P. Teriete, J.M. Asara, B.E. Turk, N.D.P. Cosford, R.J. Shaw, Small Molecule Inhibition of the Autophagy Kinase ULK1 and Identification of ULK1 Substrates, Mol. Cell. 59 (2015) 285–297. doi:10.1016/j.molcel.2015.05.031.

[36] R.C. Russell, Y. Tian, H. Yuan, H.W. Park, Y.-Y. Chang, J. Kim, H. Kim, T.P. Neufeld, A. Dillin, K.-L. Guan, ULK1 induces autophagy by phosphorylating Beclin-1 and activating VPS34 lipid kinase, Nat. Cell Biol. 15 (2013) 741–750. doi:10.1038/ncb2757.

[37] Y.-M. Kim, C.H. Jung, M. Seo, E.K. Kim, J.-M. Park, S.S. Bae, D.-H. Kim, mTORC1 Phosphorylates UVRAG to Negatively Regulate Autophagosome and Endosome Maturation, Mol. Cell. 57 (2015) 207–218. doi:10.1016/j.molcel.2014.11.013.

[38] J. Diao, R. Liu, Y. Rong, M. Zhao, J. Zhang, Y. Lai, Q. Zhou, L.M. Wilz, J. Li, S. Vivona, R.A. Pfuetzner, A.T. Brunger, Q. Zhong, ATG14 promotes membrane tethering and fusion of autophagosomes to endolysosomes, Nature. 520 (2015) 563–566. doi:10.1038/nature14147.

[39] J.A. Martina, Y. Chen, M. Gucek, R. Puertollano, MTORC1 functions as a transcriptional regulator of autophagy by preventing nuclear transport of TFEB, Autophagy. 8 (2012) 903–914. doi:10.4161/auto.19653.

[40] J. Kim, M. Kundu, B. Viollet, K.-L. Guan, AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1, Nat. Cell Biol. 13 (2011) 132–141. doi:10.1038/ncb2152.

[41] Y. Wei, S. Pattingre, S. Sinha, M. Bassik, B. Levine, JNK1-Mediated Phosphorylation of Bcl-2 Regulates Starvation-Induced Autophagy, Mol. Cell. 30 (2008) 678–688. doi:10.1016/j.molcel.2008.06.001.

[42] Y. Wei, Z. Zou, N. Becker, M. Anderson, R. Sumpter, G. Xiao, L. Kinch, P. Koduru, C.S. Christudass, R.W. Veltri, N.V. Grishin, M. Peyton, J. Minna, G. Bhagat, B. Levine, EGFR-Mediated Beclin 1 Phosphorylation in Autophagy Suppression, Tumor Progression, and Tumor Chemoresistance, Cell. 154 (2013) 1269–1284. doi:10.1016/j.cell.2013.08.015.

[43] I. Vergne, V. Deretic, The role of PI3P phosphatases in the regulation of autophagy, FEBS Lett. 584 (2010) 1313–1318. doi:10.1016/j.febslet.2010.02.054.

[44] P.-M. Wong, Y. Feng, J. Wang, R. Shi, X. Jiang, Regulation of autophagy by coordinated action of mTORC1 and protein phosphatase 2A, Nat. Commun. 6 (2015) 8048. doi:10.1038/ncomms9048.

[45] D.L. Medina, S.D. Paola, I. Peluso, A. Armani, D.D. Stefani, R. Venditti, S. Montefusco, A. Scotto-Rosato, C. Prezioso, A. Forrester, C. Settembre, W. Wang, Q. Gao, H. Xu, M. Sandri, R. Rizzuto, M.A.D. Matteis, A. Ballabio, Lysosomal calcium signalling regulates autophagy through calcineurin and TFEB, Nat. Cell Biol. 17 (2015) 288–299. doi:10.1038/ncb3114.

[46] R.V. Iozzo, M.A. Gubbiotti, Extracellular matrix: The driving force of mammalian diseases, Matrix Biol. (2018). doi:10.1016/j.matbio.2018.03.023.

[47] A. Naba, K.R. Clauser, H. Ding, C.A. Whittaker, S.A. Carr, R.O. Hynes, The extracellular matrix: Tools and insights for the “omics” era, Matrix Biol. 49 (2016) 10–24. doi:10.1016/j.matbio.2015.06.003.

[48] C. Fung, R. Lock, S. Gao, E. Salas, J. Debnath, Induction of Autophagy during Extracellular Matrix Detachment Promotes Cell Survival, Mol. Biol. Cell. 19 (2008) 797–806. doi:10.1091/mbc.E07-10-1092.

[49] T. Neill, L. Schaefer, R.V. Iozzo, Instructive Roles of Extracellular Matrix on Autophagy, Am. J. Pathol. 184 (2014) 2146–2153. doi:10.1016/j.ajpath.2014.05.010.

[50] S. Buraschi, T. Neill, R.V. Iozzo, Decorin is a devouring proteoglycan: Remodeling of intracellular catabolism via autophagy and mitophagy, Matrix Biol. (2017). doi:10.1016/j.matbio.2017.10.005.

[51] S.R. Lamandé, J.F. Bateman, Collagen VI disorders: Insights on form and function in the extracellular matrix and beyond, Matrix Biol. (2017). doi:10.1016/j.matbio.2017.12.008.

[52] M.A. Gubbiotti, T. Neill, H. Frey, L. Schaefer, R.V. Iozzo, Decorin is an autophagy-inducible proteoglycan and is required for proper in vivo autophagy, Matrix Biol. 48 (2015) 14–25. doi:10.1016/j.matbio.2015.09.001.

[53] P. Grumati, L. Coletto, P. Sabatelli, M. Cescon, A. Angelin, E. Bertaggia, B. Blaauw, A. Urciuolo, T. Tiepolo, L. Merlini, N.M. Maraldi, P. Bernardi, M. Sandri, P. Bonaldo, Autophagy is defective in collagen VI muscular dystrophies, and its reactivation rescues myofiber degeneration, Nat. Med. 16 (2010) 1313–1320. doi:10.1038/nm.2247.

[54] M. Ponpuak, M.A. Mandell, T. Kimura, S. Chauhan, C. Cleyrat, V. Deretic, Secretory autophagy, Curr. Opin. Cell Biol. 35 (2015) 106–116. doi:10.1016/j.ceb.2015.04.016.

[55] M.F. Young, Skeletal biology: Where matrix meets mineral, Matrix Biol. 52–54 (2016) 1–6. doi:10.1016/j.matbio.2016.04.003.

[56] J. Melrose, C. Shu, J.M. Whitelock, M.S. Lord, The cartilage extracellular matrix as a transient developmental scaffold for growth plate maturation, Matrix Biol. 52–54 (2016) 363–383. doi:10.1016/j.matbio.2016.01.008.

[57] A.D. Theocharis, N.K. Karamanos, Proteoglycans remodeling in cancer: Underlying molecular mechanisms, Matrix Biol. (2017). doi:10.1016/j.matbio.2017.10.008.

[58] M.D. Shoulders, R.T. Raines, COLLAGEN STRUCTURE AND STABILITY, Annu. Rev. Biochem. 78 (2009) 929–958. doi:10.1146/annurev.biochem.77.032207.120833.

[59] R. Morello, Osteogenesis imperfecta and therapeutics, Matrix Biol. (2018). doi:10.1016/j.matbio.2018.03.010.

[60] M. Kamper, N. Hamann, C. Prein, H. Clausen-Schaumann, Z. Farkas, A. Aszodi, A. Niehoff, M. Paulsson, F. Zaucke, Early changes in morphology, bone mineral

density and matrix composition of vertebrae lead to disc degeneration in aged collagen IX −/− mice, Matrix Biol. 49 (2016) 132–143. doi:10.1016/j.matbio.2015.09.005.

[61] J. Spranger, A. Winterpacht, B. Zabel, The type II collagenopathies: a spectrum of chondrodysplasias, Eur. J. Pediatr. 153 (1994) 56–65.

[62] S. Ito, K. Nagata, Biology of Hsp47 (Serpin H1), a collagen-specific molecular chaperone, Semin. Cell Dev. Biol. 62 (2017) 142–151. doi:10.1016/j.semcdb.2016.11.005.

[63] V. Malhotra, P. Erlmann, The pathway of collagen secretion, Annu. Rev. Cell Dev. Biol. 31 (2015) 109–124. doi:10.1146/annurev-cellbio-100913-013002.

[64] R. Venditti, T. Scanu, M. Santoro, G. Di Tullio, A. Spaar, R. Gaibisso, G.V. Beznoussenko, A.A. Mironov, A. Mironov, L. Zelante, M.R. Piemontese, A. Notarangelo, V. Malhotra, B.M. Vertel, C. Wilson, M.A. De Matteis, Sedlin controls the ER export of procollagen by regulating the Sar1 cycle, Science. 337 (2012) 1668–1672. doi:10.1126/science.1224947.

[65] W. Ma, J. Goldberg, TANGO1/cTAGE5 receptor as a polyvalent template for assembly of large COPII coats, Proc. Natl. Acad. Sci. U. S. A. 113 (2016) 10061–10066. doi:10.1073/pnas.1605916113.

[66] R.S. Bienkowski, S.F. Curran, R.A. Berg, Kinetics of intracellular degradation of newly synthesized collagen, Biochemistry (Mosc.). 25 (1986) 2455–2459.

[67] R.J. McAnulty, G.J. Laurent, Collagen synthesis and degradation in vivo. Evidence for rapid rates of collagen turnover with extensive degradation of newly synthesized collagen in tissues of the adult rat, Coll. Relat. Res. 7 (1987) 93–104.

[68] Y. Ishida, A. Yamamoto, A. Kitamura, S.R. Lamandé, T. Yoshimori, J.F. Bateman, H. Kubota, K. Nagata, Autophagic elimination of misfolded procollagen aggregates in the endoplasmic reticulum as a means of cell protection, Mol. Biol. Cell. 20 (2009) 2744–2754. doi:10.1091/mbc.E08-11-1092.

[69] Y. Masago, A. Hosoya, K. Kawasaki, S. Kawano, A. Nasu, J. Toguchida, K. Fujita, H. Nakamura, G. Kondoh, K. Nagata, The molecular chaperone Hsp47 is essential for cartilage and endochondral bone formation, J Cell Sci. 125 (2012) 1118–1128. doi:10.1242/jcs.089748.

[70] L. Cinque, A. Forrester, R. Bartolomeo, M. Svelto, R. Venditti, S. Montefusco, E. Polishchuk, E. Nusco, A. Rossi, D.L. Medina, R. Polishchuk, M.A. De Matteis, C.

Settembre, FGF signalling regulates bone growth through autophagy, Nature. 528 (2015) 272–275. doi:10.1038/nature16063.

[71] C.C. Dibble, B.D. Manning, Signal integration by mTORC1 coordinates nutrient input with biosynthetic output, Nat. Cell Biol. 15 (2013) 555–564. doi:10.1038/ncb2763.

[72] Y. Zhang, B. Stefanovic, mTORC1 phosphorylates LARP6 to stimulate type I collagen expression, Sci. Rep. 7 (2017). doi:10.1038/srep41173.

[73] J. Wei, J. Shimazu, M.P. Makinistoglu, A. Maurizi, D. Kajimura, H. Zong, T. Takarada, T. Iezaki, J.E. Pessin, E. Hinoi, G. Karsenty, Glucose Uptake and Runx2 Synergize to Orchestrate Osteoblast Differentiation and Bone Formation, Cell. 161 (2015) 1576–1591. doi:10.1016/j.cell.2015.05.029.

[74] J. Chen, F. Long, mTORC1 signaling controls mammalian skeletal growth through stimulation of protein synthesis, Dev. Camb. Engl. 141 (2014) 2848–2854. doi:10.1242/dev.108811.

[75] X. Wang, H. Qi, Q. Wang, Y. Zhu, X. Wang, M. Jin, Q. Tan, Q. Huang, W. Xu, X. Li, L. Kuang, Y. Tang, X. Du, D. Chen, L. Chen, FGFR3/fibroblast growth factor receptor 3 inhibits autophagy through decreasing the ATG12-ATG5 conjugate, leading to the delay of cartilage development in achondroplasia, Autophagy. 11 (2015) 1998–2013. doi:10.1080/15548627.2015.1091551.

[76] S. Bernales, S. Schuck, P. Walter, ER-phagy: selective autophagy of the endoplasmic reticulum, Autophagy. 3 (2007) 285–287.

[77] P. Grumati, G. Morozzi, S. Hölper, M. Mari, M.-L.I. Harwardt, R. Yan, S. Müller, F. Reggiori, M. Heilemann, I. Dikic, Full length RTN3 regulates turnover of tubular endoplasmic reticulum via selective autophagy, ELife. 6 (2017) e25555. doi:10.7554/eLife.25555.

[78] A. Khaminets, T. Heinrich, M. Mari, P. Grumati, A.K. Huebner, M. Akutsu, L. Liebmann, A. Stolz, S. Nietzsche, N. Koch, M. Mauthe, I. Katona, B. Qualmann, J. Weis, F. Reggiori, I. Kurth, C.A. Hübner, I. Dikic, Regulation of endoplasmic reticulum turnover by selective autophagy, Nature. 522 (2015) 354–358. doi:10.1038/nature14498.

[79] M.D. Smith, M.E. Harley, A.J. Kemp, J. Wills, M. Lee, M. Arends, A. von Kriegsheim, C. Behrends, S. Wilkinson, CCPG1 Is a Non-canonical Autophagy Cargo Receptor

Essential for ER-Phagy and Pancreatic ER Proteostasis, Dev. Cell. 44 (2018) 217-232.e11. doi:10.1016/j.devcel.2017.11.024.

[80] F. Fumagalli, J. Noack, T.J. Bergmann, E. Cebollero, G.B. Pisoni, E. Fasana, I. Fregno, C. Galli, M. Loi, T. Soldà, R. D'Antuono, A. Raimondi, M. Jung, A. Melnyk, S. Schorr, A. Schreiber, L. Simonelli, L. Varani, C. Wilson-Zbinden, O. Zerbe, K. Hofmann, M. Peter, M. Quadroni, R. Zimmermann, M. Molinari, Translocon component Sec62 acts in endoplasmic reticulum turnover during stress recovery, Nat. Cell Biol. 18 (2016) 1173–1184. doi:10.1038/ncb3423.

[81] D.N. Hebert, M. Molinari, In and out of the ER: protein folding, quality control, degradation, and related human diseases, Physiol. Rev. 87 (2007) 1377–1408. doi:10.1152/physrev.00050.2006.

[82] G.B. Pisoni, M. Molinari, Five Questions (with their Answers) on ER-Associated Degradation, Traffic Cph. Den. 17 (2016) 341–350. doi:10.1111/tra.12373.

[83] T. Hidvegi, M. Ewing, P. Hale, C. Dippold, C. Beckett, C. Kemp, N. Maurice, A. Mukherjee, C. Goldbach, S. Watkins, G. Michalopoulos, D.H. Perlmutter, An autophagy-enhancing drug promotes degradation of mutant alpha1-antitrypsin Z and reduces hepatic fibrosis, Science. 329 (2010) 229–232. doi:10.1126/science.1190354.

[84] S.A. Houck, H.Y. Ren, V.J. Madden, J.N. Bonner, M.P. Conlin, J.A. Janovick, P.M. Conn, D.M. Cyr, Quality control autophagy degrades soluble ERAD-resistant conformers of the misfolded membrane protein GnRHR, Mol. Cell. 54 (2014) 166–179. doi:10.1016/j.molcel.2014.02.025.

[85] G. Parenti, G. Andria, A. Ballabio, Lysosomal Storage Diseases: From Pathophysiology to Therapy, Annu. Rev. Med. 66 (2015) 471–486. doi:10.1146/annurev-med-122313-085916.

[86] F.M. Platt, Emptying the stores: lysosomal diseases and therapeutic strategies, Nat. Rev. Drug Discov. 17 (2018) 133–150. doi:10.1038/nrd.2017.214.

[87] L.A. Clarke, C.E.M. Hollak, The clinical spectrum and pathophysiology of skeletal complications in lysosomal storage disorders, Best Pract. Res. Clin. Endocrinol. Metab. 29 (2015) 219–235. doi:10.1016/j.beem.2014.08.010.

[88] F.M. Platt, B. Boland, A.C. van der Spoel, The cell biology of disease: lysosomal storage disorders: the cellular impact of lysosomal dysfunction, J. Cell Biol. 199 (2012) 723–734. doi:10.1083/jcb.201208152.

[89] Y.C. Wong, D. Ysselstein, D. Krainc, Mitochondria–lysosome contacts regulate mitochondrial fission via RAB7 GTP hydrolysis, Nature. 554 (2018) 382–386. doi:10.1038/nature25486.

[90] J. Xiong, M.X. Zhu, Regulation of lysosomal ion homeostasis by channels and transporters, Sci. China Life Sci. 59 (2016) 777–791. doi:10.1007/s11427-016-5090-x.

[91] W. Ge, D. Li, Y. Gao, X. Cao, The Roles of Lysosomes in Inflammation and Autoimmune Diseases, Int. Rev. Immunol. 34 (2014). doi:10.3109/08830185.2014.936587.

[92] A.P. Lieberman, R. Puertollano, N. Raben, S. Slaugenhaupt, S.U. Walkley, A. Ballabio, Autophagy in lysosomal storage disorders, Autophagy. 8 (2012) 719–730. doi:10.4161/auto.19469.

[93] R. Bartolomeo, L. Cinque, C.D. Leonibus, A. Forrester, A.C. Salzano, J. Monfregola, E.D. Gennaro, E. Nusco, I. Azario, C. Lanzara, M. Serafini, B. Levine, A. Ballabio, C. Settembre, mTORC1 hyperactivation arrests bone growth in lysosomal storage disorders by suppressing autophagy, J. Clin. Invest. 127 (2017) 3717–3729. doi:10.1172/JCI94130.

[94] P.T. Newton, K.K. Vuppalapati, T. Bouderlique, A.S. Chagin, Pharmacological inhibition of lysosomes activates the MTORC1 signaling pathway in chondrocytes in an autophagy-independent manner, Autophagy. 11 (2015) 1594–1607. doi:10.1080/15548627.2015.1068489.

[95] K. Matsunaga, T. Saitoh, K. Tabata, H. Omori, T. Satoh, N. Kurotori, I. Maejima, K. Shirahama-Noda, T. Ichimura, T. Isobe, S. Akira, T. Noda, T. Yoshimori, Two Beclin 1-binding proteins, Atg14L and Rubicon, reciprocally regulate autophagy at different stages, Nat. Cell Biol. 11 (2009) 385–396. doi:10.1038/ncb1846.

[96] Y. Zhong, Q.J. Wang, X. Li, Y. Yan, J.M. Backer, B.T. Chait, N. Heintz, Z. Yue, Distinct regulation of autophagic activity by Atg14L and Rubicon associated with Beclin 1-phosphatidylinositol-3-kinase complex, Nat. Cell Biol. 11 (2009) 468–476. doi:10.1038/ncb1854.

[97] X. Cheng, X. Ma, X. Ding, L. Li, X. Jiang, Z. Shen, S. Chen, W. Liu, W. Gong, Q. Sun, Pacer Mediates the Function of Class III PI3K and HOPS Complexes in Autophagosome Maturation by Engaging Stx17, Mol. Cell. 65 (2017) 1029-1043.e5. doi:10.1016/j.molcel.2017.02.010.

[98] P. Jiang, T. Nishimura, Y. Sakamaki, E. Itakura, T. Hatta, T. Natsume, N. Mizushima, The HOPS complex mediates autophagosome-lysosome fusion through interaction with syntaxin 17, Mol. Biol. Cell. 25 (2014) 1327–1337. doi:10.1091/mbc.E13-08-0447.

[99] J.-A. Lim, L. Li, O.S. Shirihai, K.M. Trudeau, R. Puertollano, N. Raben, Modulation of mTOR signaling as a strategy for the treatment of Pompe disease, EMBO Mol. Med. 9 (2017) 353–370. doi:10.15252/emmm.201606547.

[100] A. Fraldi, F. Annunziata, A. Lombardi, H.-J. Kaiser, D.L. Medina, C. Spampanato, A.O. Fedele, R. Polishchuk, N.C. Sorrentino, K. Simons, A. Ballabio, Lysosomal fusion and SNARE function are impaired by cholesterol accumulation in lysosomal storage disorders, EMBO J. 29 (2010) 3607–3620. doi:10.1038/emboj.2010.237.

[101] J.M. Heppner, F. Zaucke, L.A. Clarke, Extracellular matrix disruption is an early event in the pathogenesis of skeletal disease in mucopolysaccharidosis I, Mol. Genet. Metab. 114 (2015) 146–155. doi:10.1016/j.ymgme.2014.09.012.

[102] T. Koehne, S. Markmann, M. Schweizer, N. Muschol, R.E. Friedrich, C. Hagel, M. Glatzel, B. Kahl-Nieke, M. Amling, T. Schinke, T. Braulke, Mannose 6-phosphate-dependent targeting of lysosomal enzymes is required for normal craniofacial and dental development, Biochim. Biophys. Acta. 1862 (2016) 1570–1580. doi:10.1016/j.bbadis.2016.05.018.

[103] Y. Zhang, F. Vasheghani, Y.-H. Li, M. Blati, K. Simeone, H. Fahmi, B. Lussier, P. Roughley, D. Lagares, J.-P. Pelletier, J. Martel-Pelletier, M. Kapoor, Cartilage-specific deletion of mTOR upregulates autophagy and protects mice from osteoarthritis, Ann. Rheum. Dis. 74 (2015) 1432–1440. doi:10.1136/annrheumdis-2013-204599.

[104] T. Bouderlique, K.K. Vuppalapati, P.T. Newton, L. Li, B. Barenius, A.S. Chagin, Targeted deletion of Atg5 in chondrocytes promotes age-related osteoarthritis, Ann. Rheum. Dis. 75 (2016) 627–631. doi:10.1136/annrheumdis-2015-207742.

[105] M. Ito, T. Yurube, K. Kakutani, K. Maeno, T. Takada, Y. Terashima, Y. Kakiuchi, Y. Takeoka, S. Miyazaki, R. Kuroda, K. Nishida, Selective interference of mTORC1/RAPTOR protects against human disc cellular apoptosis, senescence, and extracellular matrix catabolism with Akt and autophagy induction, Osteoarthritis Cartilage. 25 (2017) 2134–2146. doi:10.1016/j.joca.2017.08.019.

[106] T. Matsuzaki, O. Alvarez-Garcia, S. Mokuda, K. Nagira, M. Olmer, R. Gamini, K. Miyata, Y. Akasaki, A.I. Su, H. Asahara, M.K. Lotz, FoxO transcription factors modulate autophagy and proteoglycan 4 in cartilage homeostasis and osteoarthritis, Sci. Transl. Med. 10 (2018). doi:10.1126/scitranslmed.aan0746.

[107] C. Pan, M.S. Nelson, M. Reyes, L. Koodie, J.J. Brazil, E.J. Stephenson, R.C. Zhao, C. Peters, S.B. Selleck, S.E. Stringer, P. Gupta, Functional abnormalities of heparan sulfate in mucopolysaccharidosis-I are associated with defective biologic activity of FGF-2 on human multipotent progenitor cells, Blood. 106 (2005) 1956–1964. doi:10.1182/blood-2005-02-0657.

[108] C. Settembre, E. Arteaga-Solis, M.D. McKee, R. de Pablo, Q. Al Awqati, A. Ballabio, G. Karsenty, Proteoglycan desulfation determines the efficiency of chondrocyte autophagy and the extent of FGF signaling during endochondral ossification, Genes Dev. 22 (2008) 2645–2650. doi:10.1101/gad.1711308.

[109] H.A. Watson, R.J. Holley, K.J. Langford-Smith, F.L. Wilkinson, T.H. van Kuppevelt, R.F. Wynn, J.E. Wraith, C.L.R. Merry, B.W. Bigger, Heparan Sulfate Inhibits Hematopoietic Stem and Progenitor Cell Migration and Engraftment in Mucopolysaccharidosis I, J. Biol. Chem. 289 (2014) 36194–36203. doi:10.1074/jbc.M114.599944.

Figure legend:

Figure 1: Proposed mechanisms of collagen regulation by the lysosome. **a**: The lysosome/autophagy pathway controls the ER homeostasis via ER-phagy and exerts a quality control role for newly synthesized procollagen molecules. In addition, the transcription of collagen genes is modulated according to the lysosome and autophagy status. The lysosome may also regulate collagen synthesis via mTORC1. **b:** Lysosomal dysfunction, such as the one observed in patients displaying lysosomal storage disorders, may perturb collagen proteostasis by impairing collagen quality control, ER homeostasis and collagen transcription and synthesis.

Highlights:

- **The lysosome/autophagy pathway has a collagen quality control role.**
- **Lysosome and autophagy dysfunctions impair collagen homeostasis and secretion.**
- **Defective collagen matrix formation contributes to the skeletal defects observed in LSDs.**

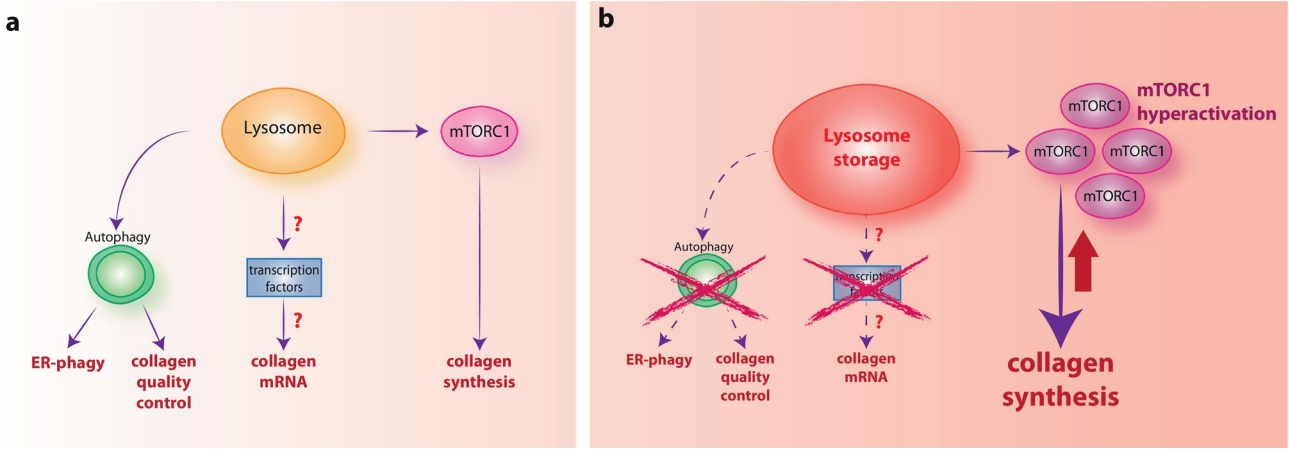
a
Lysosome
mTORC1
Autophagy
?
transcription factors
?
ER-phagy
collagen quality control
collagen mRNA
collagen synthesis
b
Lysosome storage
mTORC1
mTORC1 hyperactivation
mTORC1
mTORC1
mTORC1
Autophagy
?
?
ER-phagy
collagen quality control
collagen mRNA
collagen synthesis

Figure 1