

The Lysosome -A Central Hub for Cellular Function and Dysfunction

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Commentary

During the last decades our knowledge of the versatile tasks of the lysosome has increased tremendously. Several ground breaking discoveries, have positioned the lysosome as one of the central organelles for normal physiological function and in disease. In this short overview we exemplify some of the recent achievements in our understanding of lysosomal function during nutrient sensing, cell death, exocytosis and cholesterol homeostasis as well as lysosomal malfunction during disease. Outlined are also several of the gaps in our knowledge and challenges that need to be addressed in the future.

The Diverse Functions of the Lysosome

The endo-lysosomal system is central for cellular degradation and recycling of material delivered by endocytosis, phagocytosis and autophagy [1-3]. The lysosome is the major digestive compartment and contains around 60 hydrolases, active in the acidic environment and able to degrade most cellular macromolecules. In the lysosomal membrane integral membrane proteins are embedded, whose functions are essential for lysosomal biogenesis, acidification, transportation of metabolites, as well as chaperone-mediated autophagy. Over 45 lysosomal membrane proteins have been identified and bioinformatics analysis predicts that the list will grow in the future [4,5]. The lysosome-associated membrane protein 1 (LAMP-1) and LAMP-2 are the most abundant and constitute approximately 50% of all proteins transverse the membrane. In addition, channels and transporters of ions such as H⁺, Ca²⁺, Na⁺, K⁺, and Cl⁻ have been identified. The ion flux across the lysosomal membrane is technical difficult to study. However, a novel lysosome patch-clamping technique has been developed, making it possible to examine lysosomal channels under near physiological conditions [6]. The diverse functions of the lysosome renders it a central position not only for degradation activity, but also as a regulator of nutrient sensing, exocytosis, receptor recycling and regulation, cell death and cholesterol homeostasis [7]. Beside conventional lysosomes, lysosome related organelles (LRO), including melanosomes, lytic granules, and platelet-dense granules, exists in certain cell types and have acquired special functions [8,9].

Lysosomes have a central role in sensing the nutrient availability and generate an adaptive response to maintain cellular homeostasis [10]. This is achieved through activation of the transcription factor EB (TFEB), which occurs at the lysosomal surface and is regulated by mechanistic target of rapamycin (mTOR)-mediated phosphorylation [11]. Upon amino acid shortage, lysosomal Ca²⁺ stores are activated and released leading to activation of calcinurin, which binds and dephosphorylates TFEB, thus promoting its nuclear translocation [12]. Discovery of TFEB as a master regulator of lysosomal biogenesis, regulator of autophagic function and energy metabolism has opened a

new field of research to tie environmental alterations to lysosomal function.

Plasma membrane damage jeopardizes the survival of the cell. By translocation of lysosomes to the wounded area and donation of lysosomal membrane by exocytosis, cell lysis can be avoided [13,14]. The exocytosis process is triggered by Ca²⁺ influx from the extracellular compartment and requires the ubiquitously expressed lysosomal membrane protein synaptotagmin VII [15]. Moreover, in a model for the lysosomal disorder sialidosis, it was found that lysosomal exocytosis is increased in cells defective in neuraminidase, which results in over-sialylation of LAMP-1 [16]. The plasma membrane repair process is associated with release of lysosomal content including lysosomal proteases, cathepsins, outside the cell [17], which might have consequences for communication between cells and stimulate degradation of the basement membrane in tumors. Exocytosis is followed by removal of the lysosomal membrane by either endocytosis or a membrane shedding processes [17,18]. Lysosomes are transported along microtubules in the peripheral cytoplasm by the action of a multi-subunit complex named BORC [19]. Not all lysosomes are prone to be exocytosed upon plasma membrane damage. It is, however, not clarified how different populations of lysosomes are selected and targeted for different functions. It has been shown that lysosomes located at cell periphery are exocytosed in response to cholesterol depletion [20]. Moreover, in cancer misrouting of the lysosomes from their normal perinuclear intracellular position to the edges of the cell might facilitate exocytosis and metastatic spread [21].

Due to their high content of hydrolytic enzymes, lysosomes are potentially harmful to cells and massive lysosomal rupture might lead to necrotic cell death [22]. However partial and selective lysosomal membrane permeabilization (LMP) could trigger several forms of controlled cell death [23]. The main lysosomal players implicated in cell death are the cathepsins that are released to the cytosol during LMP [24-26]. Kreuzaler et al. recently demonstrated that LMP is not only an *in vitro* phenomenon, since the lysosome-mediate cell death pathway is active during involution of the mammary gland after lactation [27]. The mechanism of LMP is not clarified and most likely, lysosomal destabilization is due to alteration in both lysosomal membrane proteins and lipids causing destabilization of the membrane. It is also hypothesized that release of lysosomal content to the cytosol not always signals death, but might also take part in cellular signaling during normal processes.

The importance of lysosomes in cholesterol homeostasis was identified through the disease Niemann-Pick type C, which is an hereditary disorder caused by the inability to export low density lipoprotein (LDL)-derived cholesterol out of the lysosome [28,29]. In blood cholesterol is transported in LDL particles that enter the endo-lysosomal compartment by binding to the LDL receptor at the cell

surface, which is followed by endocytosis of the receptor complex. Digestion of LDL by lysosomal hydrolases liberates cholesterol, which is delivered to other cellular membranes through the action of the proteins NPC1 and NPC2 by a not yet fully defined mechanism [30]. Cholesterol intercalates between saturated hydrocarbon chains of phospholipids and may alter the physicochemical properties of the membrane. Thus, lysosomal cholesterol content is able to influence both sensitivity to LMP and lysosomal exocytosis [20,31]. Interestingly, filoviruses such as the Ebola virus enter human cells after binding *via* the cytosolic tail of NPC1 pointing to lysosomal proteins being novel therapeutic targets for combating devastating infectious diseases [32].

Lysosomal Alterations in Disease

Advances in lysosome research have expanded the understanding of the role of lysosomes in the pathophysiology of diseases. The lysosomal storage diseases (LSD) include approximately 70 distinct disorders and are characterized by a progressive accumulation of undegraded specific substrates within the organelle due to deficiency of proteins involved in lysosomal function or biogenesis [33]. Although individually rare, LSD collectively account for 14% of all inherited metabolic diseases. LSD are challenging to diagnose due to the rarity of the diseases and the heterogeneity of disease manifestations. Noteworthy, recent studies have observed that lysosomal alterations and malfunction also occur in several common pathological conditions such as cancer and neurodegenerative diseases. In brains from patients suffering from rare early-onset lysosomal storage diseases, similar neurodegenerative hallmarks are observed as in late-onset neurodegenerative diseases such as Alzheimer's and Parkinson's diseases [34]. Moreover, patients suffering from the LSD Gaucher disease have a higher risk of developing Parkinson's disease [35], indicating a possible link between these disorders. Neuronal ceroid liposuscinogenesis 11 arises due to mutations in both alleles of progranulin, whereas frontotemporal dementia occurs when a single allele is mutated [36]. A theory of a general mechanism of dysfunctional clearance of cellular cargo through the secretory-endosomal-autophagic-lysosomal-exocytic (SEALE) network has been formed to explain the common underlying feature relating lysosomal dysfunction to seemingly different diseases [34]. In addition, a toolkit utilizing next generation sequencing (NSG) for identification of DNA sequence variations in genes involved in autophagy-lysosomal pathways was recently developed and named Lysoplex. The specific selection of DNA regions belonging to about 900 genes of the autophagy-lysosomal pathway will improve the identification of genetic heterogeneity and facilitated diagnosis [37]. To treat LSD as well as common neurodegenerative diseases strategies for increasing the rate of lysosomal degradation and clearance are needed. Possible approaches that have been explored are to increase cathepsin activity by suppression of cystatins, the endogenous inhibitors of cysteine cathepsins [38], activation of TFEB [39] and suppression of neuronal cell death by prevention of LMP through upregulation of HSP70 [40], or cholesterol modulation [31]. In addition lysosomal clearance may be enhanced by increased lysosomal acidification [41].

Cancer progression and metastasis are associated with striking alterations in lysosomal compartments and tumor cells are highly dependent on effective lysosomal function. Thus, elevated expression of wildtype TFEB protein has been found sufficient for driving the oncogenic mechanism [42]. Altered activity and location of lysosomal proteases is central in tumors. Secretion of cathepsins into the extracellular space can promote tumor growth through their proteolytic effect on the basement membrane and activation of pro-

tumorigenic proteins [43]. On the other hand, cathepsin activity inside the cell is linked to tumor growth inhibition. Cancer cells resistant towards traditional therapies may be sensitive to agents that trigger LMP and engage lysosomal cell death pathways [44,45]. Moreover, several examples of passive ion trapping of hydrophobic weak bases within lysosomes have been found. The effect of such lysosomal sequestration of chemotherapeutic agents could reduce the accessibility of these drugs to their target sites [46], whereas cationic amphiphilic drugs that inhibit acid sphingomyelinase may selectively kill cancer cells by promoting ceramide-mediated cell death [47]. Several examples of lysosome-targeted drug delivery system for efficient killing of cancer cells have been suggested. Anticancer drugs might be loaded into liposomes and then directed and enriched in lysosomes through chemical modification as exemplified by conjugation of the lysosomotropic octadecyl-rhodamine B [48] or guanidinylated neomycin (GNeo) [49]. Moreover, sorbitol scaffold is easily taken up by cells and can deliver anticancer drugs that are released by cleavage of peptides that are substrates of cathepsin B [50]. Furthermore the lysosomotropic detergent O-methyl-serine dodecylamide hydrochloride (MSDH), which show a pH dependent assembly and disassembly, might be loaded with drugs at neutral pH that is released when the vesicle reaches the acidic pH of the lysosome [51].

Taken together, a wide range of possible disruptions in lysosomal function have been identified which implies the central position of the lysosome in pathogenic processes. It points to the importance of developing therapeutics targeted toward these mechanisms. Although several recent important achievements in our understanding of lysosomal function, the challenge how to use the knowledge to improve future therapeutic treatment of diseases still remains.

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