The Lysosome - A Central Hub for Cellular Function and Dysfunction

Karin Öllinger1 and Hanna Appelqvist2
1Experimental Pathology, Department of Clinical and Experimental Medicine, Sweden
2Department of Physics, Chemistry and Biology, Linköping University, Linköping, Sweden

Corresponding author: Karin Öllinger, Experimental Pathology, Department of Clinical and Experimental Medicine, Linköping University, 58185 Linköping, Sweden, Tel: +46 1328 6837; E-mail: karin.ollinger@liu.se

Received date: Jan 27, 2017; Accepted date: April 03, 2017; Published date: April 14, 2017

Copyright: © 2017 Öllinger K, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

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 hydrolyses, 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 transversing 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 calcineurin, which binds and dephosphorylates TFEB, thus promoting its nuclear translocation [12]. Discovery of TFEB as a master regulator of lysosomal biogenesis, regulator of autphagic 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 facilitat 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 lipofuscinogenesis 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 is dependent on the basement membrane and activation of pro-

1. **References**