Journal of Cell Signaling
ISSN: 2576-1471
Öllinger and Appelqvist, J Cell Signal 2017, 2:2
Commentary Open Access

The Lysosome -A Central Hub for Cellular Function and Dysfunction

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

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 transversing the membrane. In addition, channels and transporters of ions such as H^+, Ca^{2+}, 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 Ca^{2+} 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 Ca^{2+} 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 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.

References

1. de Duve C (2005) The lysosome turns fifty. Nat Cell Biol 7: 847-849.
2. Saftig P, Klumperman J (2009) Lysosome biogenesis and lysosomal membrane proteins: trafficking meets function. Nat Rev Mol Cell Biol 10: 623–635.
3. Luzio JP, Pryor PR, Bright NA (2007) Lysosomes: fusion and function. See comment in PubMed Commons below Nat Rev Mol Cell Biol 8: 622-632.
4. Schröder BA, Wrocklage C, Hasilik A, Saftig P (2010) The proteome of lysosomes. Proteomics 10: 4053-4076.
5. Chapel A, Kieffer-Jaquinod S, Sagné C, Verdon Q, Ivaldi C, et al. (2013) An extended proteome map of the lysosomal membrane reveals novel potential transporters. Mol Cell Proteomics 12: 1572-1588.
6. Xu H, Delling M, Li L, Dong X, Clapham DE (2007) Activating mutation in a mucolipin transient receptor potential channel leads to melanocyte loss in varitint-waddler mice. Proc Natl Acad Sci USA 104: 18321–18326.
7. Appelqvist H, Wäster P, Kågedal K, Öllinger K (2013) The lysosome: from waste bag to potential therapeutic target. J Mol Cell Biol 5: 214-226.
8. Dell'Angelica EC, Mullins C, Caplan S, Bonifacino JS (2000) Lysosome-related organelles. FASEB J 14: 1265-1278.
9. Luzio JP, Hackmann Y, Dieckmann NM, Griffiths GM (2014) The biogenesis of lysosomes and lysosome-related organelles. Cold Spring Harb Perspect Biol 6: a016840.
10. Sardiello M, Palmieri M, di Ronza A, Medina DL, Valenza M, et al. (2009) A gene network regulating lysosomal biogenesis and function. Science 325: 473-477.
11. Zoncu R, Bar-Peled L, Efeyan A, Wang S, Sancak Y, et al. (2011) mTORC1 senses lysosomal amino acids through an inside-out mechanism that requires the vacuolar H(+)-ATPase. Science 334: 678-683.

12. Medina DL, Di Paola S, Peluso I, Armani A, De Stefani D, et al. (2015) Lysosomal calcium signalling regulates autophagy through calcineurin and TFEB. Nat Cell Biol 17: 288-299.
13. Jaiswal JK, Andrews NW, Simon SM (2002) Membrane proximal lysosomes are the major vesicles responsible for calcium-dependent exocytosis in nonsecretory cells. J Cell Biol 159: 625-635.
14. Andrews NW, Almeida PE, Corrotte M (2014) Damage control: cellular mechanisms of plasma membrane repair. Trends Cell Biol 24: 734-742.
15. Reddy A, Caler EV, Andrews NW (2001) Plasma membrane repair is mediated by Ca(2+)-regulated exocytosis of lysosomes. Cell 106: 157-169.
16. Yogalingam G, Bonten EJ, van de Vlekkert D, Hu H, Moshiach S, et al. (2008) Neuraminidase 1 is a negative regulator of lysosomal exocytosis. Dev Cell 15: 74-86.
17. Tam C, Idone V, Devlin C, Fernandes MC, Flannery A, et al. (2010) Exocytosis of acid sphingomyelinase by wounded cells promotes endocytosis and plasma membrane repair. J Cell Biol 189: 1027-1038.
18. Wäster P, Eriksson I, Vainikka L, Rosdahl I, Öllinger K (2016) Extracellular vesicles are transferred from melanocytes to keratinocytes after UVA irradiation. Sci Rep 6: 27890.
19. Pu J, Schindler C, Jia R, Jarnik M, Backlund P, et al. (2015) BORC, a multisubunit complex that regulates lysosome positioning. Dev Cell 33: 176-188.
20. Hissa B, Pontes B, Roma PM, Alves AP, Rocha CD, et al. (2013) Membrane cholesterol removal changes mechanical properties of cells and induces secretion of a specific pool of lysosomes. PLoS One. 8: e82988.
21. Hämälistö S, Jäättelä M (2016) Lysosomes in cancer-living on the edge (of the cell). Curr Opin Cell Biol 39: 69-76.
22. De Duve C, Wattiaux R (1966) Functions of lysosome. Annu Rev Physiol 28: 435-492.
23. Boya P, Kroemer G (2008) Lysosomal membrane permeabilization in cell death. Oncogene 27: 6434-6451.
24. Roberg K, Öllinger K (1998) Oxidative stress causes relocation of the lysosomal enzyme cathepsin D with ensuing apoptosis in neonatal rat cardiomyocytes. Am J Pathol 152: 1151-1156.
25. Guicciardi ME, Gores GJ (2009) Life and death by death receptors. FASEB J 23: 1625-1637.
26. Repnik U, Hafner ÄŒesen M, Turk B (2014) Lysosomal membrane permeabilization in cell death: concepts and challenges. Mitochondrion 19 Pt A: 49-57.
27. Kreuzaler PA, Staniszewska AD, Li W, Omidvar N, Kedjouar B, et al. (2011) Stat3 controls lysosomal-mediated cell death in vivo. Nat Cell Biol 13: 303-309.
28. Johansson AC, Appelqvist H, Nilsson C, Kågedal K, Roberg K, et al. (2010) Regulation of apoptosis-associated lysosomal membrane permeabilization. Apoptosis 15: 527-540.
29. Carstea ED, Morris JA, Coleman KG, Loftus SK, Zhang D, et al. (1997) Niemann-Pick C1 disease gene: homology to mediators of cholesterol homeostasis. Science 277: 228-231.
30. Chang TY, Chang CC, Ohgami N, Yamauchi Y (2006) Cholesterol sensing, trafficking, and esterification. Annu Rev Cell Dev Biol 22: 129-157.
31. Appelqvist H, Sandin L, Björnström K, Saftig P, Garner B, et al. (2012) Sensitivity to lysosome-dependent cell death is directly regulated by lysosomal cholesterol content. PLoS One 7: e50262.
32. Gong X, Qian H, Zhou X, Wu J, Wan T, et al. (2016) Structural Insights into the Niemann-Pick C1 (NPC1)-Mediated Cholesterol Transfer and Ebola Infection. Cell 165: 1467-1478.
33. Bellettato CM, Scarpa M (2010) Pathophysiology of neuropathic lysosomal storage disorders. J Inherit Metab Dis 33: 347-362.
34. Boland B, Platt FM (2015) Bridging the age spectrum of neurodegenerative storage diseases. Best Pract Res Clin Endocrinol Metab 29: 127-143.
35. Beavan MS, Schapira AH (2013) Glucocerebrosidase mutations and the pathogenesis of Parkinson disease. Ann Med 45: 511-521.
36. Smith KR, Damiano J, Franceschetti S, Carpenter S, Canafoglia L, et al. (2012) Strikingly different clinicopathological phenotypes determined by progranulin-mutation dosage. Am J Hum Genet 90: 1102-1107.
37. Di Fruscio G, Schulz A, De Cegli R, Savarese M, Mutarelli M, et al. (2015) Lysoplex: An efficient toolkit to detect DNA sequence variations in the autophagy-lysosomal pathway. Autophagy 11: 928-938.
38. Sun B, Zhou Y, Halabisky B, Lo I, Cho SH, et al. (2008) Cystatin C-cathepsin B axis regulates amyloid beta levels and associated neuronal deficits in an animal model of Alzheimer's disease. Neuron 60: 247-257.
39. Decressac M, Mattsson B, Weikop P, Lundblad M, Jakobsson J, et al. (2013) TFEB-mediated autophagy rescues midbrain dopamine neurons from a-synuclein toxicity. Proc Natl Acad Sci USA 110: E1817–E1826.
40. Kirkegaard T, Roth AG, Petersen NH, Mahalka AK, Olsen OD, et al. (2010) Hsp70 stabilizes lysosomes and reverts Niemann-Pick disease-associated lysosomal pathology. Nature 463: 549-553.
41. Avrahami L, Farfara D, Shaham-Kol M, Vassar R, Frenkel D, et al. (2013) Inhibition of GSK-3 ameliorates ß-amyloid(A-ß) pathology and restores lysosomal acidification and mTOR activity in the Alzheimer's disease mouse model: in vivo and in vitro studies. J Biol Chem 288: 1295–1306.
42. Palmieri M, Impey S, Kang H, di Ronza A, Pelz C, et al. (2011) Characterization of the CLEAR network reveals an integrated control of cellular clearance pathways. Hum Mol Gene 20: 3852–3866.
43. Saftig P, Sandhoff K (2013) Cancer: Killing from the inside. Nature 502: 312-313.
44. Groth-Pedersen L, Jäättelä M (2013) Combating apoptosis and multidrug resistant cancers by targeting lysosomes. Cancer Lett 332: 265-274.
45. Fehrenbacher N, Gyrd-Hansen M, Poulsen B, Felbor U, Kallunki T, et al. (2004) Sensitization to the lysosomal cell death pathway upon immortalization and transformation. Cancer Res 64: 5301-5310.
46. Zhitomirsky B, Assaraf YG (2016) Lysosomes as mediators of drug resistance in cancer. Drug Resist Updat 24: 23-33.
47. Petersen NH, Olsen OD, Groth-Pedersen L, Ellegaard AM, Bilgin M, et al. (2013). Transformation-associated changes in sphingolipid metabolism sensitize cells to lysosomal cell death induced by inhibitors of acid sphingomyelinase. Cancer Cell 24: 379-393.
48. Koshkaryev A, Thekkedath R, Pagano C, Meerovich I, Torchilin VP (2011) Targeting of lysosomes by liposomes modified with octadecyl-rhodamine B. J Drug Target 19: 606-614.
49. Wexselblatt E, Esko JD, Tor Y (2015) GNeosomes: Highly Lysosomotropic Nanoassemblies for Lysosomal Delivery. ACS Nano 9: 3961-3968.
50. Maniganda S, Sankar V, Nair JB, Raghu KG, Maiti KK (2014) A lysosome-targeted drug delivery system based on sorbitol backbone towards efficient cancer therapy. Org Biomol Chem 12: 6564-6569.
51. Villamil Giraldo AM, Fyrner T, Wennmalm S, Parikh A, Öllinger K, et al. (2016) Spontaneous vesiculation and pH-induced disassembly of a lysosomotropic detergent: impacts on lysosomotropism and lysosomal delivery. Langmuir in press.