How shall I eat thee?

Klionsky, Daniel J.; Cuervo, Ana Maria; Dunn, Jr.; Levine, Beth; Klei, Ida van der; Seglen, Per O.

Published in:
Autophagy

Publication date:
2007

[Autophagy 3:5, 413-416; September/October 2007]; ©2007 Landes Bioscience

Editor's Corner

How Shall I Eat Thee?

Daniel J. Klionsky[1,*]
Ana Maria Cuervo[2]
William A. Dunn, Jr.[3]
Beth Levine[4]
Ida van der Klei[5]
Per O. Seglen[6]

[1]Life Sciences Institute and Departments of Molecular, Cellular and Developmental Biology and Biological Chemistry; University of Michigan; Ann Arbor, Michigan USA

[2]Department of Anatomy and Structural Biology; Marion Bessin Liver Research Center; Albert Einstein College of Medicine; Bronx, New York USA

[3]Department of Anatomy and Cell Biology; University of Florida College of Medicine; Gainesville, Florida USA

[4]Departments of Internal Medicine and Microbiology; University of Texas Southwestern Medical Center; Dallas, Texas USA

[5]Molecular Cell Biology; Groningen Biomolecular Sciences and Biotechnology Institute; University of Groningen; Haren, The Netherlands

[6]Proteomics Section DNR; Department of Cell Biology; Institute for Cancer Research; Rikshospitalet-Radiumhospitalet HF; University of Oslo; Oslo, Norway

*Correspondence to: Daniel J. Klionsky; University of Michigan; Life Sciences Institute; Rm. 6036; 210 Washtenaw Ave.; Ann Arbor, Michigan 48109-2216 USA; Tel.: 734.615.6556; Fax: 734.763.6492; Email: klionsky@umich.edu

Original manuscript submitted: 05/04/07
Manuscript accepted: 05/15/07
4377

KEY WORDS

autophagy, mitophagy, pexophagy, protein degradation, stress, xenophagy

"*All the cell's a stage, and all the cytoplasm in it merely a substrate for autophagy.*"
From *As You Eat It* in *Shakespeare for the Cell Biologist*

If you work in the field of autophagy we do not really need to tell you that this research area has grown tremendously. Along with that growth has developed a need for some unification of the nomenclature. In 2003, researchers working with the yeast model system proposed the use of the acronym *ATG* to denote AuTophaGy-related genes,[1] and this designation has also been adopted for most of the genes involved in autophagy in higher eukaryotes. Similarly, a common nomenclature for isoforms of lysosome associated protein type 2 (LAMP-2) was recently proposed, hopefully reducing some of the confusion resulting from the use of multiple names.[2] At this time we thought it worthwhile to consider the terms being used to describe different types of lysosomal or vacuolar degradative pathways. Many names are being introduced, and this is reasonable to the extent that these various processes have distinct features; each unique process needs a specific name to avoid confusion, and to eliminate the need for a lengthy description. It would be helpful, however, if the community agreed on their use. Finally, the addition or use of a name that implies a unique process must be backed up by data that justify the nomenclature. Thus, researchers should verify that a process is specific before using a name that implies specificity. For example, to demonstrate selectivity in organelle degradation it is incumbent upon the researcher to show that the organelle in question, and not other organelles, is sequestered and/or degraded with kinetics that distinguish it from a bulk, nonspecific process.

There are many types of autophagy. To our knowledge, the term "autophagy" (from the Greek "auto" for "self" and "phagein" meaning "to eat") was first used in a 1963 review article by Christian de Duve.[3] The first reference we have found in a research paper is in regard to a possible role of autophagy in lung cancer;[4] however, as this work was published in an Italian journal, we are not able to comment on this in any authoritative manner. The following year, de Duve published a highly referenced review,[5] and by this time the authors unquestionably refer to the process of macroautophagy, although the actual term was introduced later.[6] Perhaps the most distinguishing feature of macroautophagy for the purposes of this discussion is that it involves the generally nonspecific (see ref. 7 for an exception) sequestration of cytoplasm within a non-lysosomal/vacuolar compartment, usually delimited by a double or multiple membrane; this compartment is typically referred to as an autophagosome.

Another long-standing term that has not seen tremendous usage of late, but that is experiencing renewed interest, is "crinophagy" that is derived from the Greek "crin" meaning, "to secrete". As far as we can tell this name also derives from de Duve.[8] "Crinophagy" was originally used to describe the direct fusion of secretory vesicles with lysosomes (e.g., see refs. 9–11), resulting in the formation of a "crinosome."[12] This topic has attracted recent attention because of possible connections with diabetes, as crinophagy appears to be used for the regulated degradation of vesicle-stored insulin.[13] It is not known whether insulin degradation incorporates any aspects of macroautophagy, but that possibility has not been ruled out. We suggest that we retain the use of the term "crinophagy" as it was originally described; if it turns out that the degradation of insulin does involve a macroautophagic process, we think we will need to introduce another name. We note that "insulinophagy" should be avoided because the target of degradation would presumably be the vesicles that contain insulin rather than the hormone itself. One possibility would be "secrephagy" to note that the target is secretory vesicles, or alternatively "macrocrinophagy."

There is probably no controversy about the use or meaning of the name "chaperone-mediated autophagy" (CMA),[14] which is a process involving the direct translocation of

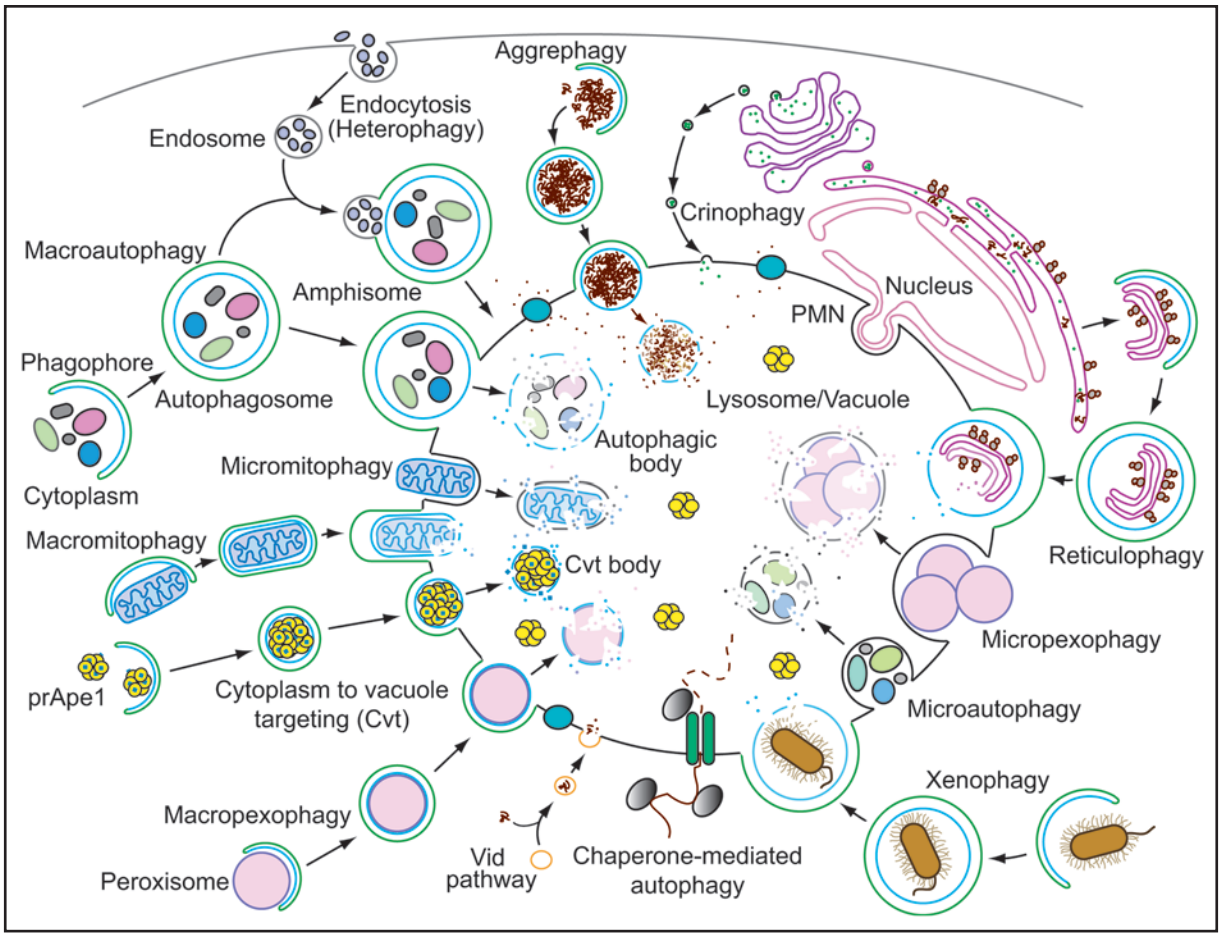

Figure 1. A schematic drawing of degradative pathways involving the lysosomal/vacuolar systems; the model depicts aspects of yeasts and higher eukaryotes. Compartments and proteins are not drawn to scale. The amphisome is a convergence point between endocytosis and autophagy. PMN, piecemeal microautophagy of the nucleus; Vid, vacuole import and degradation. See text for additional information.

proteins into the lysosome in an hsc70-mediated manner. Similarly, the term "microautophagy" does not need anything in the way of further definition at this time, although that is largely because we do not know very much about it. The "vacuole import and degradation" (Vid) pathway is a type of degradative process used for the selective turnover of fructose-1,6-bisphosphatase.[15] There is no controversy about the name of this process, and the only confusion stems from the apparent fact that fructose-1,6-bisphosphatase is degraded by an autophagy-like pathway as well as via the proteasome, depending on the specific growth conditions.[16] Portions of the nucleus can be degraded through "piecemeal microautophagy of the nucleus" (PMN),[17] whereas the "cytoplasm to vacuole targeting" (Cvt) pathway is a biosynthetic route used for the delivery of certain resident vacuolar hydrolases in yeasts.[18] These latter names are generally accepted. Accordingly, we will focus the remainder of the discussion on different types of autophagic sequestration that warrant further consideration, as well as briefly considering the history behind some of the corresponding names.

A newer term that was proposed for an autophagy-like process that is now generally accepted by researchers is "pexophagy."[19] Pexophagy, or selective peroxisome degradation through an autophagy-related mechanism, can occur through either micropexophagy or macropexophagy.[20] There is one primary point of contention regarding the use of the term "pexophagy." All researchers studying this process probably agree that when cells are shifted from conditions in which peroxisomal enzymes are needed for metabolism, such as during growth on oleic acid or methanol, to a condition in which these enzymes are no longer needed, such as growth on glucose, the process of degradation can be referred to as "pexophagy." The disagreement is whether it is correct to use this term when cells are shifted to media lacking nitrogen, as the latter condition is typically used to induce nonspecific autophagy.[21] Certainly peroxisomes can be degraded nonspecifically; however, when yeast are shifted from oleic acid to media lacking nitrogen, the kinetics and magnitude of degradation suggest a specific process.[22] Nonetheless, we may agree that the specific degradation of peroxisomes can be referred to as "pexophagy." Furthermore, the term "pexophagosome" was proposed to distinguish the sequestering vesicle from the nonspecific autophagosome.[19] Currently, pexophagy has been studied most extensively in yeasts; however, it appears that specific peroxisome degradation occurs in higher eukaryotes as well.[23,24] Therefore, we propose that the term "pexophagy" be adopted in other systems as research in this area continues.

Similar to the situation with "pexophagy," there is little reason to disagree about the use of the term "mitophagy"[25] ("mitos" is the Greek word for thread). Mitochondria can certainly be sequestered within autophagosomes during nonspecific autophagy, but the term mitophagy refers to specific degradation. The interesting feature of this term is that it has been widely accepted even though there has been relatively little evidence for the occurrence of selective

mitochondrial degradation. The first papers, to our knowledge, providing evidence of selective mitochondrial degradation in a higher eukaryote appeared in 2001;[26,27] however, more recent papers utilizing yeast have confirmed that mitochondria can be degraded through a specific process.[28-31] Some data suggest that specific degradation occurs through a microautophagic process involving direct uptake at the vacuole membrane.[29] We suggest that this be referred to as "micromitophagy," whereas engulfment via a double membrane vesicle would be "macromitophagy."

Unfortunately, this is where the clear consensus ends even though additional terms have been put forth. Among these, one quite useful term is "xenophagy"[32] (which is derived from the Greek "xenos" meaning foreign). Thus, "xenophagy" refers to the specific elimination of foreign microbes that are inside a cell, through an autophagy-related process. One criticism of this term is that it was previously used to refer to the accidental swallowing of foreign dental matter (instruments or materials);[33] however, the latter denotation was introduced over a quarter of a century ago and does not seem to have received widespread acceptance or usage. Accordingly, we suggest that this term be used in the autophagy field. Note that "xenophagy" should not be confused with the term "heterophagy," which derives from the Greek "heteros" meaning different; heterophagy was coined as a term to describe the opposite of autophagy, that is, lysosomal degradation of material not derived from self, but the term heterophagy is used to describe processes involving uptake of exogenous material by invagination of the plasma membrane, such as endocytosis and phagocytosis.

Although the reintroduction of the term "xenophagy" described work relating to bacterial degradation,[23] "xenophagy" has also been used in reference to viruses.[34] The term "virophagy" has been used in some meetings to specifically indicate the elimination of viruses through autophagy, although we are not aware of its having appeared in print in this regard; however, there are two reasons that "virophagy" is a less desirable term. First, "xenophagy" is more general and includes not only bacteria and viruses, but also fungi and parasites. Second, a recent paper uses the term "virophagy" to describe the inactivation of viruses by *Tetrahymena* that occurs in sewage water (need we say more?).[35] Therefore, we propose that the autophagy community use the term "xenophagy" as it was intended—to include the autophagic removal of any foreign microbes.

Another recently introduced term (appearing in the previous issue of this journal—you cannot get much more recent than that) is "aggrephagy"[36] (from the Latin "aggregare" meaning "add to"). This name describes the selective sequestration of protein aggregates via autophagy. Increasing evidence supports the selective enclosure of aggregates within a membrane compartment in a process that is dependent upon Atg proteins.[37] Considering the potential medical implications, it is probably worth adopting a separate name; however, we would note that the cytoprotective autophagic removal of brain cell protein aggregates may be due mainly to nonspecific macroautophagy rather than aggrephagy.[38,39]

Finally we come to one last recently published term, "ER-phagy,"[40] referring to the selective autophagic sequestration of endoplasmic reticulum membranes, which was actually the first selective autophagic process to be proposed.[41] We are not in favor of this name because it is linguistically rather awkward. Perhaps a more manageable term would be "reticulophagy" (derived from the Latin "reticulatus" for "having a net-like pattern"). Similarly, if there is specific autophagic degradation of the Golgi it seems reasonable to use "golgiphagy," which is clear in meaning and as a bonus has a certain alliterative appeal. The degradation of the entire nucleus was shown to occur through a macroautophagic process,[42] but the authors did not attempt to determine whether this was a specific process, and did not suggest a specific name. If it is specific, an obvious choice would be "nucleophagy." Finally, what happens if someone shows that lysosomes (or yeast vacuoles) can be selectively sequestered by autophagy? "Lysophagy" would seem to be a suitable name. Although once proposed, in an East German journal,[43] as a more appropriate substitute for "microautophagy," this term did not receive widespread acceptance, and can thus, with the consent of the original lead author, safely be accorded a new connotation. Alternatively, we can use the longer term "lysosomophagy"[44] that has already appeared in the literature.

SUGGESTED DEFINITIONS

Aggrephagy—the selective autophagic sequestration of protein aggregates.

Autophagy—any process involving degradative delivery of a portion of the cytoplasm to the lysosome or vacuole that does not involve direct transport through the endocytic or vacuolar protein sorting, Vps, pathways.

Chaperone-mediated autophagy (CMA)—import and degradation of soluble cytosolic proteins by chaperone-dependent, direct translocation across the lysosomal membrane.

Crinophagy—the direct fusion of secretory vesicles with lysosomes.

Cytoplasm to vacuole targeting (Cvt)—a biosynthetic pathway in yeast that transports resident hydrolases to the vacuole (the yeast lysosome) through a selective autophagy-related process.

Macroautophagy—the largely nonspecific autophagic sequestration of cytoplasm into a double- or multiple-membrane-delimited compartment (an autophagosome) of nonlysosomal/vacuolar origin. Note that certain proteins may be selectively degraded via macroautophagy, and, conversely, some cytosolic components such as cytoskeletal elements are selectively excluded.

Microautophagy—uptake and degradation of cytoplasm by invagination of the lysosomal/vacuolar membrane.

Mitophagy—the selective autophagic sequestration and degradation of mitochondria.

Pexophagy—a selective type of autophagy involving the sequestration and degradation of peroxisomes; can occur by a micro- or macropexophagic process.

Piecemeal microautophagy of the nucleus—intrusion of portions of the nucleus into the vacuole, followed by scission and degradation.

Reticulophagy—the selective autophagic sequestration and degradation of endoplasmic reticulum.

Vacuole import and degradation—the selective uptake of cytosolic fructose-1,6-bisphosphatase, and possibly other proteins, within 30 nm single membrane vesicles, followed by fusion with the vacuole and degradation.

Xenophagy—the selective degradation of microbes (e.g., bacteria, fungi, parasites and/or viruses) through an autophagy-related mechanism.

References

1. Klionsky DJ, Cregg JM, Dunn WA, Jr., Emr SD, Sakai Y, Sandoval IV, Sibirny A, Subramani S, Thumm M, Veenhuis M, Ohsumi Y. A unified nomenclature for yeast autophagy-related genes. Dev Cell 2003; 5:539-45.
2. Eskelinen E-L, Cuervo AM, Taylor MR, Nishino I, Blum JS, Dice JF, Sandoval IV, Lippincott-Schwartz J, August JT, Saftig P. Unifying nomenclature for the isoforms of the lysosomal membrane protein LAMP-2. Traffic 2005; 6:1058-61.
3. de Duve C. The lysosome. Sci Am 1963; 208:64-72.

4. Omodei Zorini A. Considerazioni sulle caverne carcinomatose primitive del polmone. Possibilita' dell'intervento di un fenomeno di "autofagismo delle cellule neoplastiche". [Considerations on primary carcinomatous caverns of the lung. Possibility of the intervention of a phenomenon of "autophagy of the neoplastic cells"]. Lotta Tuberc 1965; 35:946-68.
5. de Duve C, Wattiaux R. Functions of lysosomes. Annu Rev Physiol 1966; 28:435-92.
6. Mortimore GE, Hutson NJ, Surmacz CA. Quantitative correlation between proteolysis and macro- and microautophagy in mouse hepatocytes during starvation and refeeding. Proc Natl Acad Sci U S A 1983; 80:2179-83.
7. Onodera J, Ohsumi Y. Ald6p is a preferred target for autophagy in yeast, *Saccharomyces cerevisiae*. J Biol Chem 2004; 279:16071-6.
8. de Duve C. The lysosome in retrospect. In: Dingle JT, Fell HB, eds. Lysosomes in biology and pathology. Amsterdam and London: North Holland-Publishing Co., 1969:3.
9. Ilse G, Kovacs K, Horvath E, Ilse R, Ilse D. Lysosomal disposal of secretory granules and their transformation into pigment particles in spontaneous prolactin cell adenomas of the rat pituitary. Zeitschrift fur mikroskopisch-anatomische Forschung 1976; 90:876-82.
10. Lenk SE, Fisher DL, Dunn WA, Jr. Regulation of protein secretion by crinophagy in perfused rat liver. Eur J Cell Biol 1991; 56:201-9.
11. Marzella L, Ahlberg J, Glaumann H. Autophagy, heterophagy, microautophagy and crinophagy as the means for intracellular degradation. Virchows Archiv 1981; 36:219-34.
12. Glaumann H. Crinophagy as a means for degrading excess secretory proteins in rat liver. Revis Biol Celular 1989; 20:97-110.
13. Schnell Landström AH, Andersson A, Borg LAH. Lysosomes and pancreatic islet function: adaptation of β-cell lysosomes to various metabolic demands. Metabolism 1991; 40:399-405.
14. Massey AC, Zhang C, Cuervo AM. Chaperone-mediated autophagy in aging and disease. Curr Top Dev Biol 2006; 73:205-35.
15. Brown CR, Chiang H-L. Vacuolar import and degradation. In: Klionsky DJ, ed. Autophagy. Georgetown, TX: Landes Bioscience, 2004:176-86.
16. Hung GC, Brown CR, Wolfe AB, Liu J, Chiang H-L. Degradation of the gluconeogenic enzymes fructose-1,6-bisphosphatase and malate dehydrogenase is mediated by distinct proteolytic pathways and signaling events. J Biol Chem 2004; 279:49138-50.
17. Roberts P, Moshitch-Moshkovitz S, Kvam E, O'Toole E, Winey M, Goldfarb DS. Piecemeal microautophagy of nucleus in *Saccharomyces cerevisiae*. Mol Biol Cell 2003; 14:129-41.
18. Harding TM, Morano KA, Scott SV, Klionsky DJ. Isolation and characterization of yeast mutants in the cytoplasm to vacuole protein targeting pathway. J Cell Biol 1995; 131:591-602.
19. Klionsky DJ. Protein transport from the cytoplasm into the vacuole. J Membr Biol 1997; 157:105-15.
20. Dunn WA, Jr., Cregg JM, Kiel JAKW, van der Klei IJ, Oku M, Sakai Y, Sibirny AA, Stasyk OV, Veenhuis M. Pexophagy: the selective autophagy of peroxisomes. Autophagy 2005; 1:75-83.
21. Monastyrska I, Sjollema K, van der Klei IJ, Kiel JAKW, Veenhuis M. Microautophagy and macropexophagy may occur simultaneously in *Hansenula polymorpha*. FEBS Lett 2004; 568:135-8.
22. Hutchins MU, Veenhuis M, Klionsky DJ. Peroxisome degradation in *Saccharomyces cerevisiae* is dependent on machinery of macroautophagy and the Cvt pathway. J Cell Sci 1999; 112:4079-87.
23. Iwata J, Ezaki J, Komatsu M, Yokota S, Ueno T, Tanida I, Chiba T, Tanaka K, Kominami E. Excess peroxisomes are degraded by autophagic machinery in mammals. J Biol Chem 2006; 281:4035-41.
24. Luiken JJ, van den Berg M, Heikoop JC, Meijer AJ. Autophagic degradation of peroxisomes in isolated rat hepatocytes. FEBS Lett 1992; 304:93-7.
25. Lemasters JJ. Selective mitochondrial autophagy, or mitophagy, as a targeted defense against oxidative stress, mitochondrial dysfunction, and aging. Rejuvenation Res 2005; 8:3-5.
26. Elmore SP, Qian T, Grissom SF, Lemasters JJ. The mitochondrial permeability transition initiates autophagy in rat hepatocytes. FASEB J 2001; 15:2286-7.
27. Xue L, Fletcher GC, Tolkovsky AM. Mitochondria are selectively eliminated from eukaryotic cells after blockade of caspases during apoptosis. Curr Biol 2001; 11:361-5.
28. Kiššová I, Deffieu M, Manon S, Camougrand N. Uth1p is involved in the autophagic degradation of mitochondria. J Biol Chem 2004; 279:39068-74.
29. Kiššová I, Salin B, Schaeffer J, Bhatia S, Manon S, Camougrand N. Selective and non-selective autophagic degradation of mitochondria in yeast. Autophagy 2007; 3:329-36.
30. Zhang Y, Qi H, Taylor R, Xu W, Liu L, Jin S. The role of autophagy in mitochondria maintenance: Characterization of mitochondrial functions in autophagy deficient *S. cerevisiae* strains. Autophagy 2007; 3:337-46.
31. Priault M, Salin B, Schaeffer J, Vallette FM, di Rago JP, Martinou JC. Impairing the bioenergetic status and the biogenesis of mitochondria triggers mitophagy in yeast. Cell Death Differ 2005; 12:1613-21.
32. Levine B. Eating oneself and uninvited guests: autophagy-related pathways in cellular defense. Cell 2005; 120:159-62.
33. Samson E. Xenophagy. Br Dent J 1981; 150:136.
34. Tallóczy Z, Virgin HW, IV, Levine B. PKR-dependent autophagic degradation of herpes simplex virus type 1. Autophagy 2006; 2:24-9.
35. Pinheiro MD, Power ME, Butler BJ, Dayeh VR, Slawson R, Lee LE, Lynn DH, Bols NC. Use of *Tetrahymena thermophila* to study the role of protozoa in inactivation of viruses in water. Appl Environ Microbiol 2007; 73:643-9.
36. Øverbye A, Fengsrud M, Seglen PO. Proteomic analysis of membrane-associated proteins from rat liver autophagosomes. Autophagy 2007; 3:300-22.
37. Iwata A, Christianson JC, Bucci M, Ellerby LM, Nukina N, Forno LS, Kopito RR. Increased susceptibility of cytoplasmic over nuclear polyglutamine aggregates to autophagic degradation. Proc Natl Acad Sci U S A 2005; 102:13135-40.
38. Hara T, Nakamura K, Matsui M, Yamamoto A, Nakahara Y, Suzuki-Migishima R, Yokoyama M, Mishima K, Saito I, Okano H, Mizushima N. Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice. Nature 2006; 441:885-9.
39. Komatsu M, Waguri S, Chiba T, Murata S, Iwata J, Tanida I, Ueno T, Koike M, Uchiyama Y, Kominami E, Tanaka K. Loss of autophagy in the central nervous system causes neurodegeneration in mice. Nature 2006; 441:880-4.
40. Bernales S, McDonald KL, Walter P. Autophagy counterbalances endoplasmic reticulum expansion during the unfolded protein response. PLoS Biol 2006; 4:2311-24.
41. Bolender RP, Weibel ER. A morphometric study of the removal of phenobarbital-induced membranes from hepatocytes after cessation of threatment. J Cell Biol 1973; 56:746-61.
42. Kovács AL, Rez G, Palfia Z, Kovács J. Autophagy in the epithelial cells of murine seminal vesicle in vitro. Formation of large sheets of nascent isolation membranes, sequestration of the nucleus and inhibition by wortmannin and 3-methyladenine. Cell Tissue Res 2000; 302:253-61.
43. Seglen PO, Gordon PB, Grinde B, Solheim A, Kovács AL, Poli A. Inhibitors and pathways of hepatocytic protein degradation. Acta Biol Med Ger 1981; 40:1587-98.
44. Akahoshi M, Oshimi K, Mizoguchi H. Autophagolysosomes exhibiting lysosomophagy in the granular lymphocytes of patients with granular lymphocyte-proliferative disorders. Virchows Archiv 1993; 63:99-105.