ANTIOXIDANTS & REDOX SIGNALING
Volume 14, Number 11, 2011

DOI: 10.1089/ars.2010.3623

Autophagy: A Story of Live or Let Die

Dipak K. Das

Macroautophagy, commonly known as autophagy, involves a bulk degradation process clearing organelles, long-lived proteins, and protein complexes (18). Cytosolic constituents destined to be degraded become enclosed by double-membrane structures, known as autophagosomes or autophagic vacuoles, which are fused with lysosomes followed by the degradation of its contents (19). In fact, the process explains the term "autophagy," a housekeeping process through self-cannibalism or eating inside out.

Three types of autophagy are known to exist: (i) microautophagy involving dumping of cytosolic constituents into the lysosome by direct invagination of the lysosomal membrane followed by budding of vesicles into the lysosomal lumen; (ii) macroautophagy or autophagy involving the formation of a double membrane structure, known as autophagosome that sequesters cytosolic constituents to be delivered into the lysosomes for digestion; and (iii) chaperone mediated autophagy characterized by its selectivity of the cytosolic proteins to be degraded (8). Thus, any autophagic process undergoes four stages: (i) induction by external stress such as environmental stress (*e.g.*, oxidative stress), nutritional stress (*e.g.*, nutritional deprivation), and physical stress (*e.g.*, ischemia or hypoxia); the gatekeeper for induction is mamalian target of Repamycin, which regulates transcriptional activation of downstream target genes (16); (ii) the next stage involves autophagosome formation as described earlier where a number of Atg genes participate and recruit Beclin-1 and LC3 (14); (iii) in the third stage, autophagosomes undergo docking and fusion with the lysosome; and finally (iv) in the last stage, autophagic vesicles are broken down by lysosomal proteases, where LAMP-2 plays a crucial role in the degradation process (4).

Whether autophagy is a signal for survival or death remains under considerable debate. Since autophagy was first described in 1960, the phenomenon was associated with cell death (9). Only recently, autophagy has been known to potentiate a survival signal except that starvation has long been known to induce survival (3). It is now believed that when a cell is subjected to stress, depending on the amount of stress, the autophagy can induce a survival signal or a death signal. In that context, autophagy may be viewed as "cry for survival" and such survival is a result of adaptive response. If the stress such as oxidative stress is mild, it generates an adaptive response to survive against the stress; autophagy results in survival signal by inducing a number of genes and transcription factors that alter the stress-induced death signal into a survival signal, leading to the production of antiapoptotic and antideath proteins. If, on the other hand, the stress is overwhelming, the adaptive response fails and the cell dies due to the induction of apoptotic signals. To survive, cells must get rid of damaged and detrimental and unwanted components, and they do so through autophagy (5, 10).

The important question is then whether we can use autophagy clinically for the health benefits. The simple answer is yes, if we can control the amount of stress. There is no doubt that a small amount of stress can induce autophagy generating a survival signal, whereas the same autophagy will potentiate a death signal if the amount of such stress is large and becomes cytotoxic to the cells. Thus, we need to define a "therapeutic amount of stress" for the induction of autophagy, the same amount that has been known to induce an adaptive response for the cells subjected to hostile environment. In this Autophagy Forum, the original contributions and reviews are carefully selected to discuss all of the above-mentioned issues in a cohesive manner. This Forum on autophagy consists of two highly original articles on the use of autophagy for health benefits and seven comprehensive reviews covering the mechanisms of autophagy. In one of the original articles, Ionnis Bossis and his coworkers from Maryland describe how retinoic acid can induce autophagosome maturation through the redistribution of the cation-independent mannose-6-phosphate receptor (15). As discussed earlier, to use autophagy for health benefits, methods need to be devised to deliver therapeutic amount of stress signal, and this is a clear example of inducing maturation of autophagosomes with retinoic acid (5). The other original article of delivering therapeutic amount of stress such as oxidative stress to protect ischemic heart comes from Dipak K. Das and his group in Connecticut. Here the authors have described how clinically relevant endoplasmic reticulum (ER) stress can be generated by manipulating calcium signaling and depending on the amount of ER stress the autophagy can generate either a survival signal or a death signal (12). The mechanisms of ER stress-mediated autophagy signaling are clearly described in this article.

Seven reviews are carefully selected from the authorities of autophagy research. In one of the reviews, Bartoszewska and Kiel (2) from the Netherlands have provided a comprehensive review on the mechanisms of autophagy using yeast as a model system. They have described how a similar mechanism of action regulated autophagy in fungi. Thus, this review describes autophagy in prokaryotic system (16). Lorenzo Galluzzi and Guido Kroemer from France and Italy describe oncosuppressive functions of autophagy (11). Here

Cardiovascular Research Center, University of Connecticut School of Medicine, Farmington, Connecticut.

again beneficial and detrimental effects of stress-induced autophagy in the context of cancer are discussed. Mechanism of autophagosome formation and intracellular signaling mechanisms are reviewed by Isei Tanida (17) from Tokyo, Japan (10).

Since autophagy affects the effector cells of innate and adaptive immunity mediating the inflammatory response, its activity in these cells influences the antimicrobial response, the development of an effective cognate immune defense and the course of the normal sterile inflammatory reactions. The level of autophagic activity may determine whether tissue cells die by apoptosis, necrosis, or through autophagy and, as a consequence, whether the clearance of these dying cells is a silent process or results in an inflammatory response. Loss or decreased autophagy may lead to necrotic death, which can initiate an inflammatory reaction in phagocytes through their surface and cytosolic receptors. This least known aspect of autophagy is discussed by László Fésüs from Debrecen (13).

Two reviews are selected in the area of autophagy in cardiovascular diseases from Junichi Sadoshima from Newark (6) and Lorrie Kirshenbaum, Manitoba, Canada (1). Sadoshima and his colleagues have discussed how oxidative stress stimulates autophagic flux during myocardial ischemia and reperfusion, whereas Kirshenbaum discussed the role of mitochondria in autophagy. John Brumell from Toronto, Canada, discusses another aspect on the role of reactive oxygen species in autophagy and how it relays the signal into survival or death of the cells (7).

The editor of this Autophagy Forum expects that all the aspects of autophagy are well covered by the reviews and the two original articles are useful for using autophagy in the clinical arena with therapeutic amount of stress generating an adaptive response. It is hoped that in near future, autophagy will be used as potential therapy to cure diseases. There is no doubt that the process of autophagy in mammalian system is still in its infancy, and the major challenge is to understand the underlying mechanisms of autophagy and clearly define therapeutic amount of stress.

References

1. Aviv Y, Shaw J, Gang H, and Kirshenbaum LA. Regulation of autophagy in the heart: "You only live twice". *Antioxid Redox Signal* 14: 2245–2250, 2011.
2. Bartoszewska M and Kiel JAKW. The role of macroautophagy in development of filamentous fungi. *Antioxid Redox Signal* 14: 2271–2287, 2011.
3. Eskelinen E-L. Doctor Jekyll and Mister Hyde: autophagy can promote both cell survival and cell death. *Cell Death Differ* 12: 1468–1472, 2005.
4. Eskelinen EL, Illert AL, Yoshitaka D, Tanaka D, Schwarzmann G, Judith Blanz J, Figura KV, and Saftig P. Role of LAMP-2 in lysosome biogenesis and autophagy. *Mol Biol Cell* 13: 3355–3368, 2002.
5. Goswami SK and Das DK. Autophagy in the myocardium: dying for survival. *Exp Clin Cardiol* 11: 183–188, 2006.
6. Hariharan N, Zhai P, and Sadoshima J. Oxidative stress stimulates autophagic flux during ischemia/reperfusion. *Antioxid Redox Signal* 14: 2179–2190, 2011.
7. Huang J, Lam GY, and Brumell JH. Autophagy signaling through reactive oxygen species. *Antioxid Redox Signal* 14: 2215–2231, 2011.
8. Kiffin R, Christian C, Knecht E, and Cuervo AM. Activation of chaperone-mediated autophagy during oxidative stress. *Mol Biol Cell* 15: 4829–4840, 2004.
9. Kundu M and Thompson CB. Autophagy: basic principles and relevance to disease. *Annu Rev Pathol* 3: 427–455, 2008.
10. Mizushima N, Ohsumi Y, and Yoshimori T. Autophagosome formation in mammalian cells. *Cell Struct Funct* 27: 421–429, 2002.
11. Morselli E, Galluzzi L, Kepp O, Mariño G, Michaud M, Vitale I, Maiuri MC, and Kroemer G. Oncosuppressive functions of autophagy. *Antioxid Redox Signal* 14: 2251–2269, 2011.
12. Petrovski G, Das S, Juhasz B, Kertesz A, Tosaki A, and Das DK. Cardioprotection by endoplasmic reticulum stress–induced autophagy. *Antioxid Redox Signal* 14: 2191–2200, 2011.
13. Fésüs L, Demény MÁ, and Petrovski G. Autophagy shapes inflammation. *Antioxid Redox Signal* 14: 2233–2243, 2011.
14. Raftopoulou M. Autophagy: to die or not to die. *Nat Cell Biol* 7: 1056–1057, 2005.
15. Rajawat Y, Hilioti Z, and Bossis I. Retinoic acid induces autophagosome maturation through redistribution of the cation-independent mannose-6-phosphate receptor. *Antioxid Redox Signal* 14: 2165–2177, 2011.
16. Rosenbluth JM and Pietenpol JA. mTOR regulates autophagy-associated genes down-stream of p73. *Autophagy* 5: 114–116, 2009.
17. Tanida I. Autophagosome formation and molecular mechanism of autophagy. *Antioxid Redox Signal* 14: 2201–2214, 2011.
18. Tsujimoto Y and Shimizu S. Another way to die: autophagic programmed cell death. *Cell Death Differ* 12: 1528–1531, 2005.
19. Yorimitsu T and Klionsky DJ. Autophagy: molecular machinery for self-eating. *Cell Death Differ* 12: 1542–1552, 2005.

Address correspondence to:
Prof. Dipak K. Das
Cardiovascular Research Center
University of Connecticut School of Medicine
263 Farmington Ave.
Farmington, CT 06030-1110

E-mail: ddas@neuron.uchc.edu

Date of first submission to ARS Central, September 27, 2010; date of acceptance, October 2, 2010.

Abbreviation Used

ER = endoplasmic reticulum

This article has been cited by: