Introduction to the Thematic Minireview Series: Autophagy

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Autophagy is a highly conserved, tightly regulated cellular process that degrades intracellular constituents via lysosomes. Autophagy mediates many normal cellular functions and is dysregulated in numerous diseases. This Thematic Series consists of five Minireviews that highlight selected topics of current autophagy research ranging from the molecular mechanisms and regulation of autophagy to the roles of autophagy in health and disease.

Autophagy is a general term for several distinct but related cellular processes that result in the lysosomal degradation of cellular constituents. The magnitude of autophagy is tightly regulated by many factors characteristic of specific physiologic states. Such regulation allows cells to adapt to changing conditions by sculpting their inventory of components, including the proteome, and by providing degradation products for other uses, elimination, or recycling. Because autophagy is an embedded regulatory feature of many normal cellular functions, it is not surprising that its dysregulation is an important element of abnormal and diseased states.

Although autophagy was identified over 60 years ago as a lysosome-based morphologic process (1–3), the molecular mechanisms by which it operates remained largely unknown until Ohsumi and colleagues (4) exploited yeast genetics to identify many of its essential proteins. Their groundbreaking work, which was recognized by the 2016 Nobel Prize, provided the foundation for the subsequent elucidation of the molecular and cellular roles of these and other discovered autophagic proteins (5–7). Continuing advances by many investigators have greatly expanded our understanding of the mechanistic and regulatory complexity of autophagy and established its pervasive role in cellular and organismal physiology (8, 9). The following five Minireviews highlight selected topics related to the remarkable advances in current autophagy research.

The first two Minireviews deal with current knowledge of the molecular mechanisms of autophagy. Mercer, Gubas, and Tooze (10) describe the machinery and intricate mechanisms by which autophagosomes are initially formed. These early events in the process involve multiple essential proteins and are subject to careful regulation by physiologic signals such as the levels of certain amino acids. Delorme-Axford and Klionsky (11) continue this narrative and describe transcriptional and post-transcriptional regulation of autophagy, highlighting the complex variety of ways the process can be controlled.

The third Minireview by Grumati and Dikic (12) describes the fascinating role that ubiquitin plays in autophagy. Once considered a cardinal element of a completely separate and independent arm of the cell's mechanisms for protein destruction (the ubiquitin–proteasome system), ubiquitin is now recognized as a versatile molecule that can participate in both proteolytic systems and even has multiple roles within autophagy.

The early conception of autophagy as an inherently nonselective process has been dispelled by the discovery of multiple autophagy subtypes that selectively target certain proteins, protein complexes, or organelles for degradation. These processes highlight the versatility and regulatory power of autophagy. The fourth Minireview by Tekirdag and Cuervo (13) reviews recent progress on two of the multiple subtypes of autophagy that selectively target substrates for autophagic destruction: chaperone-mediated autophagy and endosomal microautophagy. They describe a common mechanism by which hsc70 can direct substrates to these distinct catabolic pathways.

The final Minireview addresses relationships between autophagy and disease. However, instead of reviewing the many examples of diseases linked to altered or required autophagy, Thorburn (14) presents a series of important issues to consider when addressing these relationships. This exercise provides insightful guidelines and parameters for critical evaluation of this rapidly expanding field.

Despite its long and distinguished history, autophagy remains a vibrant research area with an unabated pace of progress. This Thematic Minireview Series provides an excellent snapshot of its current state and future promises.

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