Autophagy Special Collection: Cell machinery dealing with stress and beyond

Thirty years ago, the use of genetic models to characterize the core genes involved in the process of autophagy triggered an ever-expanding research field with broad implications for how homeostasis and cell defense are regulated in health and disease (*1*, *2*). The name "autophagy" was first used in 1963 by Christian de Duve, the discoverer of lysosomes, to describe intracellular vacuoles containing lysosomal enzymes associated with bits of sequestered cytoplasm in decomposition observable by electron microscopy (*3*). Currently, canonical autophagy (also called macroautophagy or simply autophagy) refers to the packaging of cytoplasmic contents within an expanded membrane bud that folds over itself, creating a double-membrane compartment directed to fusion with lysosomes.

Because autophagy promotes clearance of cytosolic debris and elimination of intracellular invaders, it is a key process to restoring cell fitness in stress situations and, therefore, with critical functions in metabolic syndromes, cancer, neurodegeneration, and immunity to infectious diseases. Autophagy occurs in steady-state (bulk autophagy), but it is actively increased during nutritional stress or cell damage to target and eliminate protein complexes and diverse organelles (selective autophagy). Through the course of evolution, the same machinery was also selected to isolate and get rid of pathogens that invade host cell cytosol (xenophagy). The signaling cascade of autophagy is complex and involves sequential engagement of multiprotein complexes that ultimately cause conjugation of members of the autophagy-related (ATG) 8 family of small proteins to phosphatidylethanolamine phospholipid of cell membranes. ATG8 lipidation is a requirement for compartment maturation (generating an autophagosome) and for promoting the fusion of autophagosomes with lysosomes. In cell biology research, ATG8 lipidation is a hallmark of autophagy widely used to identify its occurrence.

Today, we recognize that components of the autophagy machinery can participate in alternative molecular complexes that target ATG8 lipidation to other cell compartments, with consequences beyond cargo degradation. One such example of noncanonical autophagy is the conjugation of ATG8 to single membranes (CASM), a process known to occur in compartments of the endocytic pathway formed during the engulfment of certain cargo (either by phagocytosis, endocytosis, or macropinocytosis). Events so far characterized as CASM are mostly related to the regulation of immune responses, particularly in professional phagocytes of the innate immune system. Because canonical and noncanonical autophagy shares several molecular components, reverse genetic studies using knockout mice to characterize the role of canonical autophagy in different pathologies might be CASM events. It also became clear that most bona fide components of the autophagic machinery also participate in other cell processes, varying from intracellular trafficking, exocytosis, and unconventional secretion to regulation of cell division, proliferation, and death. Finally, alternative pathways can also lead to unconventional biogenesis of canonical autophagosomes, showing that even well-characterized components of autophagy are not universally required to mediate responses to nutrient restriction.

These several layers of molecular and functional complexity for autophagic processes and the ubiquitous importance of autophagy-relevant proteins in cell physiology may help explain why modulating autophagy is not a common target in therapeutics, despite an ever-growing interest in harnessing it to treat a variety of diseases. It is essential to define their relevance in the pathophysiology of various disorders to dissect the components of the different autophagy pathways and understand when or where they are at play. It should be fundamental to modulate them in clinical settings successfully. Conversely, such efforts might provide additional therapeutic opportunities to molecular targeting specific pathways in cells of interest and bypass the possible harmful effect of disturbing core mechanisms that safeguard homeostasis and function of other cell types.

The special collection in this issue assembles five articles in which the contributing authors tackle the literature on molecular characterization of autophagic pathways and the evidence that corroborate their importance in different disorders.

Durgan and Florey (*4*) review the diverse noncanonical autophagic pathways leading to CASM—from association to endosomes during engulfment to disturbances of endolysosomal pH caused by drugs and virulence factors of intracellular pathogens. Further, they compile and analyze evidence supporting a unifying role for the regulation of the function of the V-ATPase (adenosine triphosphatase) pump that acidifies vesicles as a shared requirement between these diverse noncanonical autophagy pathways.

One example of CASM is LC3-associated endocytosis (LANDO). LANDO was first characterized in the context of

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recycling putative β-amyloid receptors in microglia cells, preventing neuroinflammation, and protecting against Alzheimer's disease in a murine model. Magne and Green (*5*) tease down the regulation of two fundamental effectors of LANDO, Rubicon and ATG16L1 (interestingly, the latter is the first *ATG* gene shown to regulate autophagy and noncanonical autophagy through different domains in its structure). The authors also explore the evidence supporting a role for LANDO in regulating innate immune responses in order disorders such as inflammatory disorders and metabolic diseases. In contrast, Choi *et al.* (*6*) explore the literature on the role of the autophagic process in the clearance of α-synonuclein protein aggregates and protection against neuroinflammation associated with Parkinson's disease. In comparison, these two articles are great examples of how autophagy proteins may have different implications for disorders with seemly similar pathogenesis.

Perhaps the best-characterized CASM phenomenon is LC3-associated phagocytosis (LAP). LAP is known to occur in response to the phagocytosis of pathogens, dead cells, and immunocomplexes. Peña-Martinez *et al.* (*7*) trace parallels and differences between LAP and LANDO pathways and their consequences for regulating immune responses and inflammation. Also, the role of noncanonical autophagy, including LAP, in infectious diseases is thoroughly reviewed by Wang *et al.* (*8*).

Thus, this compilation should give readers a broad view of the diversity of autophagic processes, the evidence to discriminate them, and why this knowledge has broad therapeutic implications.

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