

## CELL BIOLOGY

## Focus Issue: Autophagy as hero and villain

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This Focus Issue explores autophagic responses to stress in cardiometabolic disease, reveals how autophagy limits pathological hypertrophy in the heart, and describes how autophagy itself can regulate transcriptional responses to stress.

The 2016 Nobel Prize in Physiology or Medicine was awarded to Yoshinori Ohsumi for his work in identifying the genes in *Saccharomyces cerevisiae* that are critical for autophagy. In this evolutionarily conserved process, macromolecules, organelles, and invading pathogens are encapsulated into double-membrane vacuoles called autophagosomes, which fuse with lysosomes for degradation (see Simon *et al.* for the molecular details of this process). Autophagy is particularly critical during cell starvation to reclaim nutrients, during stress to eliminate damaged cellular constituents, and during infection to limit pathogen spread (see the Editors' Choice summary by VanHook). Originally thought to be a nonspecific process, extensive investigation has revealed that autophagy is a highly regulated process that intersects with many signaling pathways.

Whether autophagy is beneficial or detrimental depends on context. When nutrients are available, the protein complex mTORC1 suppresses both the initiation of autophagosome formation (see Simon *et al.* and Chan) and the transcriptional activation of genes involved in lysosomal biogenesis (see Rocznik-Ferguson *et al.* and Martina *et al.*). Starvation conditions relieve the mTORC1-mediated suppression of the autophagosome-initiating machinery and of the transcription factors critical for lysosomal biogenesis. In the nutrient-limited tumor microenvironment, cancer cells often depend on autophagy for survival, as shown by Wengrod *et al.* for melanoma and by Fan *et al.* for glioma. Thus, blocking autophagy in these contexts would be expected to suppress tumor growth. However, in breast cancer cells that are deficient in the enzyme that synthesizes arginine, the application of an arginine-metabolizing enzyme induces mitochondrial dysfunction, leading to unrestrained autophagy and cell death as shown by Qiu *et al.* Thus, in some cancer contexts, autophagy induction is tumor-suppressive (see also Ferrarelli).

Many types of cellular stress induce the accumulation of aggregated proteins or dam-

aged organelles that must be cleared to ensure cellular homeostasis and survival. The metabolic dysfunction that occurs in diseases such as obesity, diabetes, and atherosclerosis is characterized by an inability to clear these protein aggregates or damaged organelles that leads to oxidative stress, inflammation, and disease progression. The Review by Evans *et al.* describes the impairment of various forms of autophagy in the heart and metabolic diseases (collectively referred to as cardiometabolic diseases) that are so prevalent in developed nations. These include the autophagic removal of ubiquitin-tagged protein aggregates through aggrephagy, which involves the cargo receptor p62, and the elimination of damaged mitochondria by mitophagy (see also Altshuler-Keylin and Kajimura). Evans *et al.* propose that stimulating autophagy in diseases characterized by accumulation of dysfunctional organelles may be an attractive therapeutic option.

Research Articles in this issue and in the Archives, as well as those featured in Editors' Choice (see Gough), provide examples of how boosting autophagy could be clinically beneficial. In a Research Article and associated Podcast, Simonson *et al.* examined the protective role of autophagy against pathological cardiac hypertrophy, which is triggered by sustained high blood pressure and, if left untreated, leads to heart failure. They found that the expression of the gene encoding the mTORC1 inhibitor DDIT4L was increased in the heart by pathological stress but not by physiological stress (such as exercise). Cardiomyocytes that overexpressed DDIT4L were smaller than control cardiomyocytes, and the hearts of mice that overexpressed DDIT4L in a cardiac-specific fashion showed inhibited mTORC1 signaling and increased autophagy. These results collectively suggest that increasing autophagy through DDIT4L may prevent some forms of pathological cardiac hypertrophy. Enhancing autophagy could be similarly protective in nonalcoholic fatty liver disease (NAFLD) and atherosclerosis. DeBosch *et al.* (see the Focus by Mardones *et al.*) found that the natural disaccharide trehalose induces au-

tophagy that limits hepatic lipid accumulation in a mouse model of NAFLD. In atherosclerosis, macrophages produce proinflammatory cytokines that increase the number and size of plaques, and autophagy is dysfunctional in macrophages that infiltrate these plaques. Sergin *et al.* showed that enhancing p62-dependent aggrephagy in macrophages could be a way of preventing these immune cells from exacerbating atherosclerosis (see also Wong).

However, a global or even tissue-specific increase in autophagy is not always desirable. Altshuler-Keylin and Kajimura discuss how mitophagy determines the identity and function of adipocytes, of which there are three types. White adipocytes store excess energy as triglycerides, and an increase in the size of certain white adipose depots is associated with increased risk for obesity-associated diseases in humans. In contrast to white adipocytes, brown adipocytes, which are rich in mitochondria, uncouple oxidative phosphorylation to dissipate energy in the form of heat. There are also beige adipocytes, which have some of the characteristics of brown adipocytes, including abundant mitochondria and thermogenic activity. Their formation can be induced through specific stimuli, such as cold exposure or  $\beta_3$ -adrenergic receptor stimulation. Upon removal of these stimuli, the beige adipocytes behave more as white adipocytes, and Altshuler-Keylin and Kajimura describe how blocking mitophagy is crucial for the maintenance of the beige adipocyte phenotype. Thus, a nonspecific enhancement of mitophagy might have adverse metabolic consequences by shifting adipocytes from the beige to white phenotype. Enhancing autophagy can also interfere with the action of other drugs. For example, Zhang *et al.* showed that the drug verteporfin triggers the accumulation of toxic amounts of protein aggregates that selectively kill colorectal cancer cells in mice and in cells experiencing hypoxic and nutrient-deprived conditions; normal colorectal cells clear these protein aggregates through aggrephagy. In this case, increasing aggrephagy would nullify the anticancer effect of verteporfin. Autophagic processes can also contribute to tissue damage, and thus, enhancing

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autophagy can exacerbate disease in some situations. Sun *et al.* found that the H5N1 strain of avian influenza increases the number of autophagosomes in the lung and that inhibiting autophagy in infected mice reduces lung damage and mortality.

An understanding of whether autophagy in a specific context is beneficial or detrimental requires acknowledging that not only is autophagy triggered by various stresses but also that autophagy affects other aspects of cellular behavior, at least partially by altering transcriptional responses to stress. Simon *et al.* discuss this “retrograde” regulation (from autophagosome to nucleus). For example, some autophagy-related proteins bind directly to transcription factors to promote or suppress their activity. In another example, the transcription factors required for lysosomal biogenesis need autophagy-related proteins to translocate to the nucleus. Two examples, in particular, illustrate how autophagy and transcriptional stress responses can be intertwined. As described by Simon *et al.* and Evans *et al.*, the transcription factor Nrf2 mediates antioxidant responses to oxidative stress, but basally, the abundance of this transcription is kept low by Keap1, a substrate adaptor protein for a ubiquitin E3 ligase complex. By directing Keap1 to autophagosomes, p62 promotes Nrf2-dependent transcriptional responses. Another example concerns the transcription factor NF- $\kappa$ B, which promotes proinflammatory responses. Several proteins involved in the activation of NF- $\kappa$ B bind to Beclin-1, which recruits phosphoinositide 3-phosphate-generating kinases that promote autophagosome formation. Autophagy requires the release of Beclin-1 from these NF- $\kappa$ B pathway components, and autophagic flux is necessary for the activation of NF- $\kappa$ B in response to certain stimuli.

We anticipate that new regulators of autophagy will be identified, that new biological contexts in which autophagy is critical will be found, and that signals mediating the flow of information between autophagy and other cellular processes will be discovered. Researchers working on understanding the regulation of autophagy and its effects or cross-talk with signaling pathways or on the translation of such information for understanding disease pathology or developing treatment strategies are encouraged to submit to the journal.

## RELATED RESOURCES

### Reviews

- S. Altshuler-Keylin, S. Kajimura, Mitochondrial homeostasis in adipose tissue

remodeling. *Sci. Signal.* **10**, eaai9248 (2017). [Abstract]

- T. D. Evans, I. Sergin, X. Zhang, B. Razani, Target acquired: Selective autophagy in cardiometabolic disease. *Sci. Signal.* **10**, eaag2298 (2017). [Abstract]
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### Perspective

- E. Y. Chan, mTORC1 phosphorylates the ULK1-mAtg13-FIP200 autophagy regulatory complex. *Sci. Signal.* **2**, pe51 (2009). [Abstract]

### Focus

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### Podcast

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### Editors' Choice

- L. K. Ferrarelli, Overcoming immunotherapy resistance. *Sci. Signal.* **9**, ec32 (2016). [Abstract]
- N. R. Gough, TLR9 sustains autophagic flux. *Sci. Signal.* **9**, ec180 (2016). [Abstract]
- A. M. VanHook, TRIMS for autophagy. *Sci. Signal.* **7**, ec237 (2014). [Abstract]
- W. Wong, Limiting inflammation with p62. *Sci. Signal.* **9**, ec52 (2016). [Abstract]

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