

## SELF DIGESTION

Autophagy—the process by which a cell digests and recycles various molecules and organelles in its cytoplasm—is critical for maintaining homeostasis and for helping cells survive low-nutrient conditions. In a series of steps, a vesicle precursor, known as the phagophore, is formed, and cellular contents accumulate as it matures into an autophagosome. Then, after fusion with a lysosome, the inner vesicle of the autophagosome is digested along with the cargo, and the products are released into the cytoplasm. Over the past 25 years, researchers have detailed the molecular regulators of this process, with recent insights shedding light on autophagy's link to both health and disease.

### 1 PHAGOPHORE NUCLEATION

A protein kinase complex and a lipid kinase complex coordinate the recruitment of a piece of membrane that will form the basis of the phagophore. The origin of the donor membrane is unknown, but may include the endoplasmic reticulum (ER), the Golgi apparatus, or the plasma membrane.

### 2 PHAGOPHORE EXPANSION

With the help of several autophagy-related (ATG) proteins, a small, ubiquitin-like protein called LC3 (LC3-II when bound) binds the nascent phagophore to direct its expansion around cytoplasmic components to be degraded—which may be randomly selected or may include specific cargo such as damaged organelles or misfolded proteins, depending on the nature of the stress. ATG9 is a transmembrane protein that shuttles between the site of phagophore formation and peripheral membrane sites and is thought to recruit more membrane for the expanding phagophore.

### 3 AUTOPHAGOSOME FORMATION

The elongating phagophore closes to form the double-membrane autophagosome, enclosing cytoplasmic cargo targeted for degradation.

### 4 AUTOPHAGOSOME-LYSOSOME FUSION

The outer membrane of the autophagosome fuses with the membrane of the lysosome, leading to the exposure of the cargo-enclosing inner autophagosomal membrane to the hydrolases present in the lysosomal lumen. This lysosome is now called an autolysosome.

### 5 DEGRADATION AND EFFLUX

Lysosomal hydrolases degrade the inner autophagosomal membrane, and then the cargo within. Transporters known as permeases on the autolysosome membrane then move the macromolecules generated into the cytoplasm, where they can be reused by the cell.

