

HOW AUTOPHAGY WORKS

There are five steps of autophagosome biogenesis: induction, expansion, vesicle completion, fusion, and cargo degradation. While much has been learned over the past few decades about how this process works, the big question that remains is where the double lipid bilayers originate.

THE STEPS OF AUTOPHAGOSOME FORMATION

Under autophagy-inducing conditions, a membranous cistern called the phagophore—generated from the phagophore assembly site (PAS), a putative early autophagosome precursor—begins to form **A**. The acquisition of extra lipids permits the expansion of the phagophore and subsequent engulfment of the material targeted for destruction **B**. The inner and outer bilayer then fuse to form two distinct membranes, one inside the other **C**, forming the complete autophagosome. Endosomal structures fuse with the autophagosome to form amphisomes **D**, which then fuse with a lysosome (in mammals) or vacuole (in yeast and plants) **E**. Hydrolytic enzymes from each of these compartments degrade the inner membrane of the autophagosome, gaining access to the cargo of the inner vesicle **E**. Eventually, all the contents of the autophagosome are degraded, yielding basic metabolites that are transported in the cytoplasm to be reused as a source of energy or building blocks for new proteins and lipids **F**.

