about autophagy... Autophagy is a highly conserved eukaryotic pathway for sequestering and transporting bulk cytoplasm, including proteins and organelle material, to the lysosome for degradation. Upon starvation for nutrients such as carbon, nitrogen, sulfur, and various amino acids, or upon endoplasmic reticulum stress, cells initiate formation of a double-membrane vesicle, termed an autophagosome, that mediates this process. Approximately 30 autophagy-relatedproteins have been identified in S. cerevisiae, 17 of which are essential for formation of the autophagosome. Null mutations in most of these genes prevent induction of autophagy, and cells do not survive nutrient starvation; however, these mutants are viable in rich medium. Some of the Atg proteins are also involved in a constitutive biosynthetic process termed the cytoplasm-to-vacuole targetingpathway, which uses autophagosomal-like vesicles for selective transport of hydrolases aminopeptidase Iand alpha-mannosidaseto the vacuole. Autophagy proceeds via a multistep pathwaykindly provided by Dan Klionsky). First, nutrient availability is sensed by the TORC1 complex and also cooperatively by protein kinase A and Sch9p. Second, signals generated by the sensors are transmitted to the autophagosome-generating machinery comprised of the 17 Atg gene products. These 17 proteins collectively form the pre-autophagosomal structure/phagophore assembly site. The PAS generates an isolation membrane, which expands and eventually fuses along the edges to complete autophagosome formation. At the vacuole the outer membrane of the autophagosome fuses with the vacuolar membrane and autophagic bodies are released, disintegrated, and their contents degraded for reuse in biosynthesis.about autophagic ubiquitin-like conjugation Formation of autophagosomes requires a number of autophagy proteins that are involved in one of two ubiquitin-like conjugation systems, the Atg12 and Atg8 systems. The final product of these two systems is a lipidated form of Atg8p that appears to be required for membrane tethering and hemifusion, which are essential for autophagosome formation. In the Atg12 system, the ubiquitin-like protein Atg12p is activated by the E1-like enzyme Atg7p and then transferred to Atg10p, an enzyme with E2-like activity. Atg12p is then constitutively and irreversibly conjugated to Atg5p, which is the only Atg12p target. After Atg12p-Atg5p conjugation, Atg16p associates with the conjugate, resulting in a ~350kDa complex. It is hypothesized that the role of Atg16p in this complex is to properly localize the Atp12p-Atg5p conjugate, which acts as an E3-like enzyme in the Atg8 conjugation system. In the Atg8 system, the other autophagic ubiquitin-like protein Atg8p is first cleaved at its C-terminal end by the cysteine protease Atg4p, which is structurally similar to deubiquitinating enzymes. The proteolytically processed form of Atg8p is then activated by Atg7p and transferred to Atg3p, another E2-like enzyme. Finally, Atg8p is conjugated to the lipid phosphatidylethanolamine, a reaction stimulated by the E3-like activity from the Atg5p-Atg12p complex. Atg8p-PE conjugation is reversible; deconjugation is mediated by Atg4p and interferes with membrane fusion.about the Cytoplasm-to-vacuole targetingpathway Cytoplasm-to-vacuole targetingis a constitutive and specific form of autophagy that uses autophagosomal-like vesicles for selective transport of hydrolases aminopeptidase Iand alpha-mannosidaseto the vacuole. Unlike autophagy, which is primarily a catabolic process, Cvt is a biosynthetic process. Like autophagosomes, Cvt vesicles form at a structure known as the phagophore assembly site. The PAS structure generates an isolation membrane, which expands and eventually fuses along the edges to complete vesicle formation. At the vacuole, the outer membrane of the Cvt vesicle fuses with the vacuolar membrane, the vesicle is degraded, and the cargos are released and processed into their mature forms by vacuolar peptidases. The Cvt pathway has not been observed outside of yeast, and enzymes specifically involved in this pathway are not well conserved in other organisms.about ATG7 Atg7p is primarily a cytoplasmic protein but interaction with Atg12p leads to its association with membranes. Atg7p, which is involved in autophagy, the Cvt pathway, and peroxisome degradation, functions in a manner similar to the ubiquitin-activating E1 enzyme Uba1p. Moreover, the region spanning residues 322-392 has significant homology to a region of Uba1p and contains an ATP-binding domainthat is essential for the conjugation reaction. Atg7p binds to and thus activates Atg12p via a thioester bond between the C-terminal Gly186 of Atg12p and Cys507 of Atg7p. Atg7p activates Atg8p via a similar type of bond between the C-terminal glycine of Atg8p and Cys507. Null atg7 mutants lack autophagic bodies, do not form the Atg12p-Atg5p conjugate, and fail to properly import the vacuolar hydrolase aminopeptidase Iby the Cvt pathway. Overexpression of ATG7 in nitrogen stress conditions inhibits the filamentous growth response normally exhibited by cells. Atg7p function in autophagy and the Cvt pathways requires the C-terminal 17 amino acids; removal of these residues prevents lipidation of Atg8p but has no effect on Atg12p-Atg5p conjugation or Atg7p homodimerization. The human homolog of ATG7, APG7L, interacts with human ATG12 and has E1-like activity similar to the yeast homolog. Studies in mice reveal that loss of ATG7 in the central nervous system leads to neurodegeneration.about autophagy nomenclature The initial identification of factors involved in autophagy was carried out by several independent labs, which led to a proliferation of nomenclature for the genes and gene products involved. The differing gene name acronyms from these groups included APG, AUT, CVT, GSA, PAG, PAZ, and PDD. A concerted effort was made in 2003 by the scientists working in the field to unify the nomenclature for these genes, and \"AuTophaGy-related\" genes are now denoted by the letters ATG. In addition to the ATG gene names that have been assigned to S. cerevisiae proteins and their orthologs, several ATG gene names, including ATG25, ATG28, and ATG30, have been used to designate proteins in other ascomycete yeast species for which there is no identifiable equivalent in S. cerevisiae.