# REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

*John P. Lynch and David C. Metz, Section Editors*

## Functions of Autophagy in Hepatic and Pancreatic Physiology and Disease

MARK J. CZAJA

*Department of Medicine and Marion Bessin Liver Research Center, Albert Einstein College of Medicine, Bronx, New York*

**Podcast interview: www.gastro.org/gastropodcast.**

**Autophagy is a lysosomal pathway that degrades and recycles intracellular organelles and proteins to maintain energy homeostasis during times of nutrient deprivation and to remove damaged cell components. Recent studies have identified new functions for autophagy under basal and stressed conditions. In the liver and pancreas, autophagy performs the standard functions of degrading mitochondria and aggregated proteins and regulating cell death. In addition, autophagy functions in these organs to regulate lipid accumulation in hepatic steatosis, trypsinogen activation in pancreatitis, and hepatitis virus replication. This review discusses the effects of autophagy on hepatic and pancreatic physiology and the contribution of this degradative process to diseases of these organs. The discovery of novel functions for this lysosomal pathway has increased our understanding of the pathophysiology of diseases in the liver and pancreas and suggested new possibilities for their treatment.**

*Keywords:* Steatosis; Cell Death; Pancreatitis; Hepatitis Virus.

Autophagy is an intracellular pathway by which lysosomes degrade and recycle long-lived proteins and cellular organelles. This pathway degrades cellular components that are worn out or damaged or are needed to generate substrates that maintain cellular energy homeostasis under conditions of limited nutrients or stress.[1–3] Studies of the effects of altered autophagy in the liver have demonstrated the importance of the function of this pathway. In rats, a starvation-induced increase in autophagy led to the degradation of 35% of total liver protein within 24 hours.[4] Conversely, inhibition of macroautophagy, by knockout of the autophagy gene *atg7* in hepatocytes, led to a 4-fold increase in liver mass because of failure to degrade a variety of cellular components.[5] Individual organs have specific and selective functions for this lysosomal pathway. In liver and pancreas, autophagy can regulate levels of lipids and contribute to pancreatitis and viral hepatitis. Although 3 distinct autophagic pathways have been described, most studies have been on macroautophagy, and this review summarizes the basic physiologic functions of macroautophagy and their role in the pathophysiology of hepatic and pancreatic diseases.

### Autophagic Pathways

#### *Macroautophagy*

The 3 known types of autophagy are macroautophagy, chaperone-mediated autophagy (CMA), and microautophagy (Figure 1).[6,7] In macroautophagy, a portion of cytosol is engulfed by a double-membrane structure, termed an autophagosome, that fuses with a lysosome, whose enzymes degrade the cellular constituents sequestered in the autophagosome.[6] The regulation of this process is complex and controlled by the coordinated actions of autophagy-related genes (Atgs), over 30 of which have been identified in yeast and humans.[8] Studies in yeast indicated that an initial structure, called an isolation membrane or phagophore, becomes a nascent autophagosome, whose ends elongate until they form the completely enclosed autophagosome. The source of the double membrane is controversial, but it might be de-

*Abbreviations used in this paper:* AT, $\alpha_1$-antitrypsin; Atg, autophagy-related gene; ATP, adenosine triphosphate; CMA, chaperone-mediated autophagy; ER, endoplasmic reticulum; HBx, hepatitis B virus protein X; LAMP-2, lysosome-associated membrane protein 2; LC3, microtubule-associated protein 1 light chain 3; LPS, lipopolysaccharide; MPT, mitochondrial permeability transition; mTOR, mammalian target of rapamycin; p62, p62/sequestosome-1/SQSTM1; PI3K, phosphatidylinositol 3-kinase; TG, triglyceride.

© 2011 by the AGA Institute

0016-5085/$36.00
doi:10.1053/j.gastro.2011.04.038

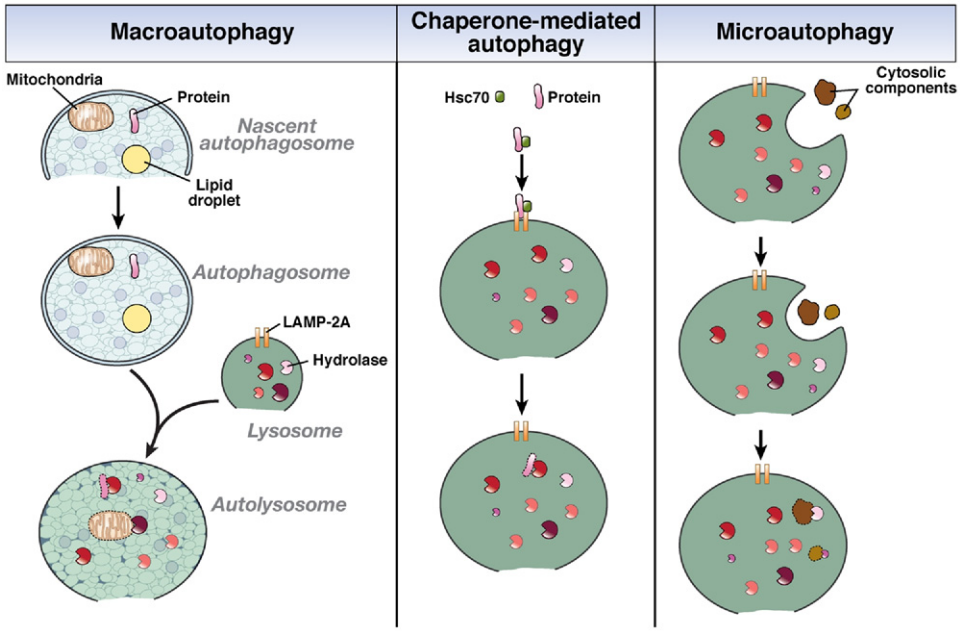


**Figure 1.** The 3 pathways of autophagy. In macroautophagy, a double membrane of unclear origin forms around cytosolic components such as mitochondria, lipid droplets, and proteins. The membrane elongates to completely enclose the cellular elements within an autophagosome that translocates to a lysosome containing degradative hydrolases. The 2 structures fuse into an autolysosome, in which the cellular components are degraded by the lysosomal hydrolases. In CMA, cytosolic proteins with a specific pentapeptide motif are recognized by the chaperone Hsc70. This complex binds to the lysosomal LAMP-2A receptor for protein internalization and proteolytic degradation. Microautophagy involves the uptake of cellular components, both organelles and proteins, within an invagination of the lysosomal membrane for enzymatic degradation in the lysosome.

rived from the endoplasmic reticulum (ER), mitochondria, or plasma membrane.[9] The double membrane of the autophagosome is formed and elongated by unclear mechanisms, but a number of multiprotein complexes are known to mediate these processes.

There are 3 major pathways that regulate macroautophagy (Figure 2). The first is the inhibitory mammalian target of rapamycin (mTOR) pathway. In direct response to nutrients (particularly amino acids), or through nutrient-induced insulin, class I phosphatidylinositol 3-kinase (PI3K) activates Akt and mTOR. This signaling pathway blocks macroautophagy through the ability of mTOR to inhibit Atg1 from recruiting its partners Atg13 and Atg17.[10] The Atg1–Atg13–Atg17 complex recruits and organizes other proteins for the developing autophagosome.[11,12] The mTOR inhibitor rapamycin is the most commonly used agent to increase autophagy; however, findings from studies with this agent cannot always be ascribed to its effects on autophagy, because mTOR regulates many other cellular pathways.[13] Another pathway that regulates autophagy is mediated by Atg6/beclin-1, which forms a complex with the class III PI3K Vps34. Activation of the Atg1–Atg13–Atg17 complex leads to organization of the beclin-1–Vps34 complex on the lipid membrane. Vps34 produces phosphatidylinositol 3-phosphate, which can recruit other proteins to the complex.[14,15] It is important to distinguish this PI3K from the insulin-activated, class I PI3K, which activates mTOR. Vps34 is the target of the widely used pharmacologic inhibitor of autophagy 3-methyladenine.[16] Beclin-1 is an important interface between the autophagic and cell death pathways, because the antiapoptotic proteins Bcl-2 and Bcl-$X_L$ bind beclin-1 to inhibit autophagy.[17] The regulation of this interaction is complex but includes its disruption by c-Jun N-terminal kinase 1–mediated phosphorylation of Bcl-2.[18]

The third major pathway that mediates autophagosome formation and elongation involves 2 ubiquitin-like conjugation processes that generate membrane-bound protein complexes. In the first, Atg7 and Atg10 mediate the conjugation of Atg12 to Atg5,[19] which subsequently interact with Atg16.[20] The Atg12–Atg5 complex associates with the membrane and then dissociates upon completion of the autophagosome. The second critical conjugation reaction involves Atg8 or microtubule-associated protein 1 light chain 3 (LC3). LC3 is constitutively cleaved by Atg4 to produce LC3-I. With a signal to induce autophagy, Atg7 and Atg3 mediate the conjugation of LC3-I to the membrane lipid phosphatidylethanolamine to form LC3-II.[21] LC3-II associates with the autophagosomal membrane, where the lipidated protein can mediate membrane elongation and closure. LC3-II is degraded late in the autophagic pathway, after autophagosome fusion with a lysosome. In immunoblot analyses, increased levels of LC3-II are often misinterpreted as conclusive evidence of increased autophagic function. Although increased levels of LC3-II can indicate an increase in autophagy, they can also reflect a decrease in au-

Download English Version:

https://daneshyari.com/en/article/3293012

Download Persian Version:

https://daneshyari.com/article/3293012

Daneshyari.com