Hepatology Snapshot

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Autophagy in the liver

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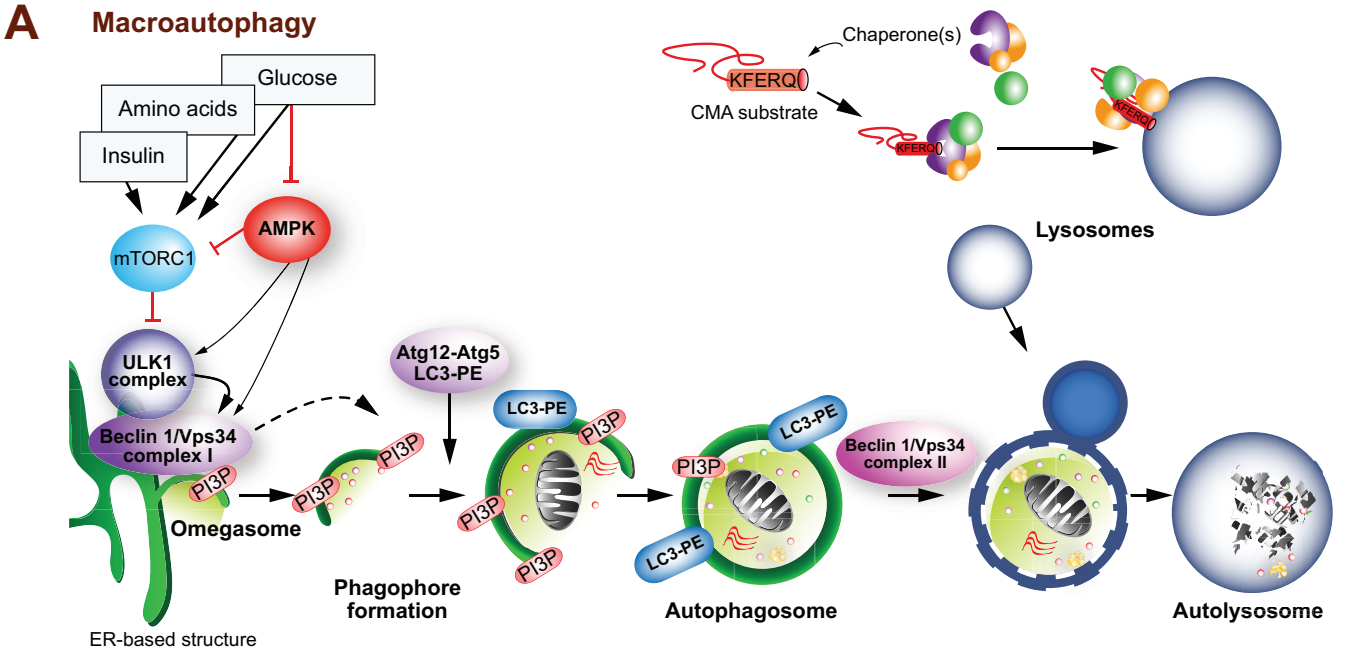

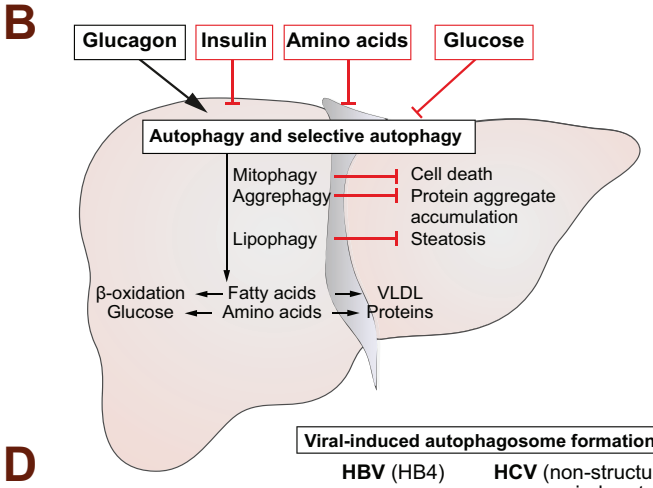

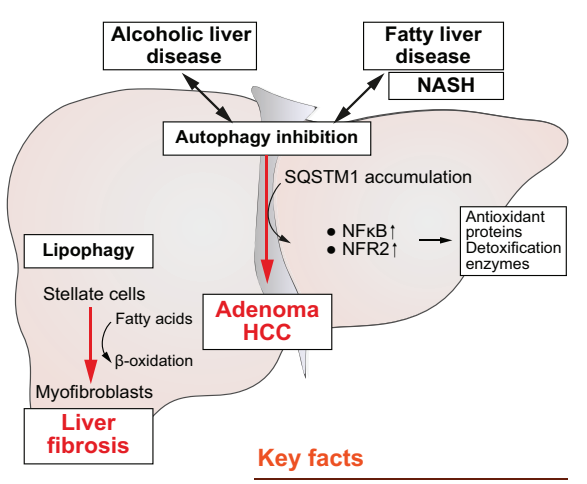

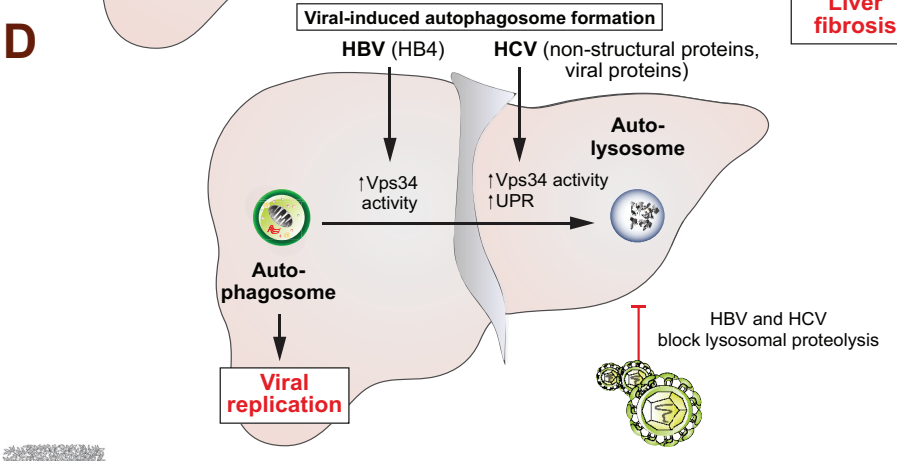

Key facts

Autophagy is required to maintain liver homeostasis
- through elimination of aggregate-prone proteins and damaged mitochondria
- by counteracting hepatocyte swelling

Genetic models have shown that inhibition of autophagy genes favors the development of liver tumors

Liver macroautophagy declines in obese mice

Acute alcohol consumption induces hepatic autophagy. By contrast, chronic alcohol consumption suppresses hepatic autophagy

Both hepatitis B and C viruses subvert autophagy for their own benefit

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Background

The term "autophagy" covers three processes responsible for the lysosomal degradation of cell components: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA) of proteins containing a KFERQ motif [1]. Macroautophagy and microautophagy can be non-selective processes, but in many cases they can also be highly selective for organelles, lipid droplets, aggregate-prone proteins, or microorganisms invading the cytoplasm. The paradigm for selective macroautophagy is the recognition of the cargo by autophagy receptors that connect the cargo to the autophagy machinery. For example, the autophagy receptor SQSTM1/p62 recognizes ubiquitinated, tagged protein aggregates *via* its ubiquitin-associated domain, and recognizes the autophagy protein microtubule-associated protein 1 light chain 3, LC3, *via* its LC3-interacting region (LIR) motif [2].

Microautophagy is the direct engulfment of cytoplasmic material by the lysosomal membrane, whereas macroautophagy starts with the formation of a double-membrane surrounded vacuole, known as the autophagosome, which ultimately fuses with the lysosomal compartment where the sequestered material is degraded. The autophagosome originates from a membrane known as the phagophore, the nucleation and elongation of which depend on the autophagy-related (*ATG*) genes, which were originally discovered in the yeast *Saccharomyces cerevisiae* and are well conserved in mammals [2]. The UNC-51-like kinase 1 ULK1 (ATG1) complex initiates phagophore formation in an endoplasmic reticulum (ER)-based structure known as the omegasome. The activity of this complex is controlled by the mammalian target of rapamycin complex 1 (mTORC1), which integrates signals from amino acids, glucose, and insulin (growth factors) [3]. Dissociation of mTORC1 from the ULK1 complex under starvation conditions initiates autophagosome formation. The ULK1 complex acts in a coordinated manner with Beclin 1 (ATG6):Vps34 (class III phosphatidylinositol 3-kinase) complex I. The production of PtdIns3P by vacuolar protein sorting 34 (Vps34) is an important trigger for the elongation and closure of the autophagosome by two ubiquitin-like conjugation systems, ATG5-ATG12 and LC3 (ATG8)-PE (phosphatidylethanolamine).

Autophagy in liver physiology and metabolism

The basal rate of macroautophagy (hereafter referred to as 'autophagy') is required to maintain liver homeostasis through the elimination of aggregate-prone proteins and damaged mitochondria and by counteracting hepatocyte swelling [4]. Blockade of basal autophagy interferes with the cell quality control and leads to hepatomegaly, which is followed by inflammation, hepatitis, and tumorigenesis. Suppression of autophagy results in the accumulation of SQSTM1, which acts as a signaling hub to activate the NF-kB signaling pathway, the transcription of genes encoding for antioxidant proteins, and detoxification enzymes via the activation of the Nrf2 transcription factor [4]. The importance of the quality control of autophagy is illustrated in the classic form of α1-antitrypsin deficiency, where the mutant protein accumulates in the ER and forms intrahepatic inclusions. By stimulating autophagy, carbamazepine reduces the severity of α1-antitrypsin deficiency in a mouse model [5]. CMA also contributes to the elimination of damaged proteins and to the maintenance of liver function [6].

During periods of fasting, autophagy contributes to gluconeogenesis, ß-oxidation of fatty acids and to ketone body formation. Amino acids used for gluconeogenesis are produced by proteolysis through bulk autophagy [3], whereas fatty acids are mainly produced by selective autophagy of triglycerides stored in lipid droplets (lipophagy) [7]. Autophagy probably also controls the level of very-low-density lipoprotein (VLDL) particles through lipophagy, which releases fatty acids and degrades apolipoprotein B. Liver autophagy plays a key role in restoring plasma glucose concentrations in neonates during fasting [8]. Liver autophagy is also hormonally controlled: insulin inhibits while glucagon stimulates the process [3]. The mTORC1 complex, together with Rag and Rheb GTPases, plays a major role in autophagy control by integrating nutritional signals. Amino acids and glucose repress autophagy via the Rag-dependent activation of mTORC1. In addition, the absence of glucose activates the AMP-activated protein kinase, which simultaneously inhibits mTORC1 and activates the ULK1 complex. Moreover, AMPK stimulates autophagy by phosphorylating Beclin 1 in the Beclin 1:Vps34 complex I [9]. Insulin and growth factors activate mTORC1 in a Rheb-dependent manner. Insulin also inhibits autophagy in an mTOR-independent manner, through, for example, transcriptional downregulation of several ATG genes. In the liver of a starved animal, autophagy declines after 24–48 h, and CMA is stimulated. The decline in the production of amino acids by bulk autophagy is associated with the decrease in gluconeogenesis at this stage [3] and ketone bodies may take part in the activation mechanism of CMA [10].

Autophagy in liver pathology

Autophagy and metabolic disease

Liver autophagy declines in obese mice. Hyperinsulinemia, hyperactivation of mTOR and downregulation of ATG5, ATG7, and Beclin 1 may all contribute to downregulation of autophagy [3,4]. Hepatic triglyceride and cholesterol contents are increased in hepatic *Atg7*-deficient mice, confirming that autophagy plays a key role in regulating hepatic lipid storage [7]. ER stress plays a crucial role in the link between obesity, liver steatosis, insulin-resistance, and type 2 diabetes. Forced expression of ATG7 in the liver of obese mice reduces ER stress, and improves glucose tolerance and insulin sensitivity. Stimulating autophagy may prevent the progression of steatosis in non-alcoholic steatohepatitis (NASH). However, the role of autophagy in obesity and insulin resistance is complex, because induction of the mitokine Fgf21 induces resistance to diet-induced obesity and improves insulin resistance in mice with hepatic autophagy deficiency [11]. Lipophagy is probably involved in the reduction of lipid droplets observed during the activation of stellate cells during the onset of liver fibrosis [12].

Acute alcohol consumption, via the production of reactive oxygen species, induces hepatic autophagy, presumably as an initial attempt to combat the toxic effect of alcohol by the selective removal of lipid droplets and damaged mitochondria [13]. By contrast, chronic alcohol consumption suppresses hepatic autophagy. This is probably the consequence of reduced AMPK activity and of the inhibition by ethanol of vesicular transport required for autophagosome formation [14]. Alcohol-induced blockade of autophagy favors the accumulation of aggregate-prone proteins, hyperactivation of Nrf2 (via the accumulation of SQSTM1/p62) and accumulation of damaged mitochondria, leading to cell death.

Autophagy and infectious diseases

Both hepatitis B and C viruses subvert autophagy for their own benefit [14]. The viral protein HBx stimulates autophagosome formation by increasing the activity of the Beclin 1:Vps34 complex, without increasing lysosomal protein degradation. Autophagy proteins and autophagy membranes are required for HBV viral replication and morphogenesis. An accumulation of autophagosomes is also observed in HCV-infected cells. The autophagy machinery promotes the initial steps in HCV replication.

Autophagy and hepatocellular carcinoma (HCC)

Genetic models have shown that inhibition of autophagy genes favors the development of liver tumors [4]. Not only do mice heterozygous for Beclin 1 show a high frequency of spontaneous HCC, they also display accelerated development of HBV-induced, small-cell dysplasia [14]. Accordingly, the expression of Beclin 1 is lower in HCC cells than in adjacent non-tumor cells. Inhibition of autophagy leads to the accumulation of SQTSM1/p62, which in turn leads to persistent activation of the NF-kB pathway and Nrf2. SQSTM1/p62 knockout markedly suppresses liver adenoma growth in mice specifically lacking Atg7 in the liver [4]. The activation of Nrf2 redirects glucose and glutamine into anabolic pathways such as the pentose phosphate pathway and purine nucleotide synthesis, which support tumor cell proliferation [15].

Fig. Autophagy in the liver. (A) The autophagic pathway. (B) Autophagy in liver metabolism. (C) Autophagy and liver disease. (D) Autophagy in liver viral infections. CMA, chaperone-mediated autophagy; LAH, lysosomal acid hydrolases; HBV, hepatitis B virus; HCV, hepatitis C virus; UPR, unfolded protein response; HCC, hepatocellular carcinoma.

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Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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