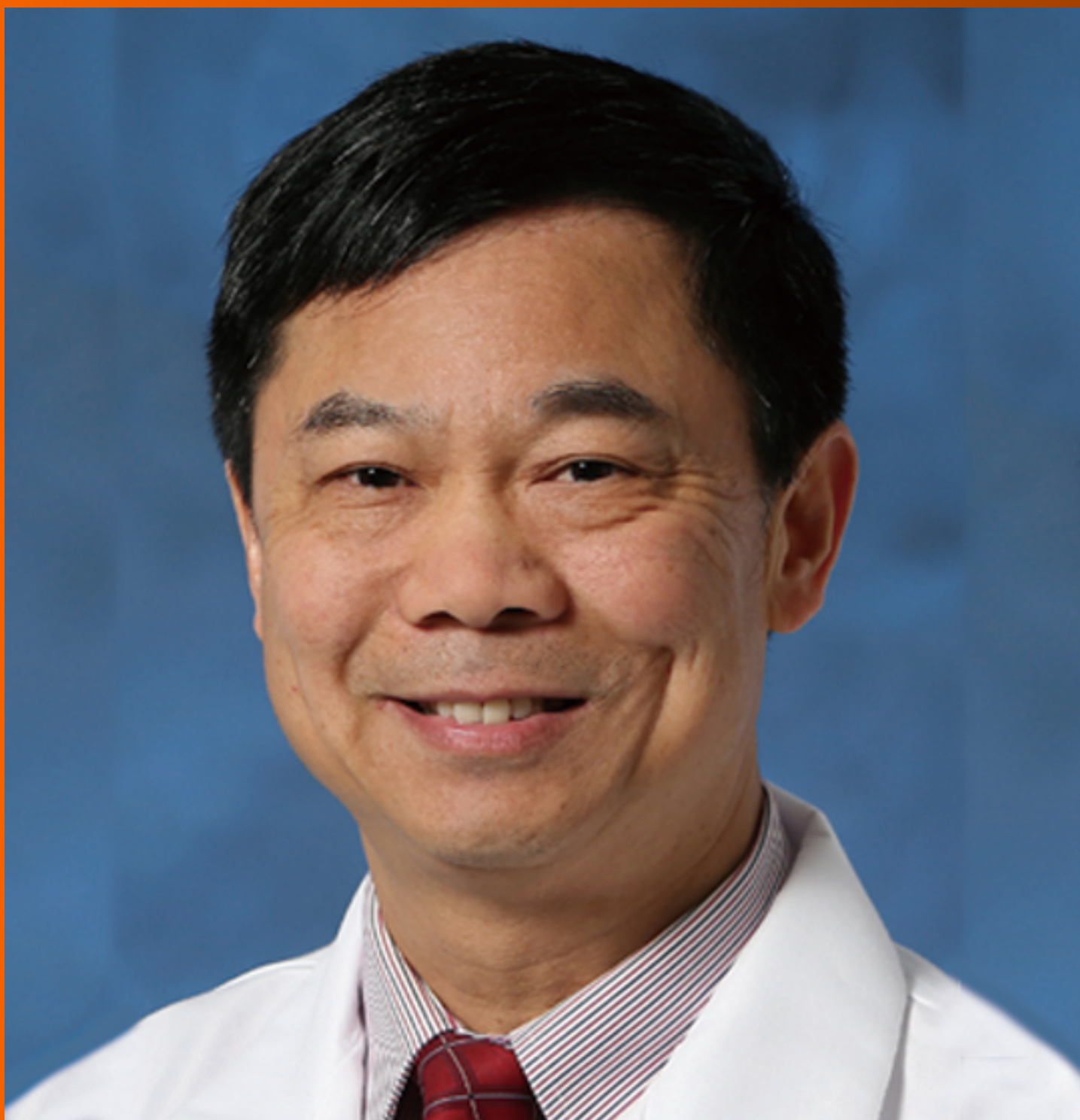


World Journal of *Hepatology*

World J Hepatol 2021 January 27; 13(1): 1-161



EDITORIAL

- 1 New Year's greeting and overview of *World Journal of Hepatology* in 2021
Hu KQ, Kang KJ, Pysopoulos N, Li X

REVIEW

- 6 Autophagy in liver diseases
Kouroumalis E, Voumvouraki A, Augoustaki A, Samonakis DN

MINIREVIEWS

- 66 Post-liver transplant biliary complications: Current knowledge and therapeutic advances
Boeva I, Karagoyozov PI, Tishkov I
- 80 Shifting perspectives – interplay between non-alcoholic fatty liver disease and insulin resistance in lean individuals
Bilic-Curcic I, Cigrovski Berkovic M, Virovic-Jukic L, Mrzljak A

ORIGINAL ARTICLE

Basic Study

- 94 Integrative analysis of layers of data in hepatocellular carcinoma reveals pathway dependencies
Bhat M, Pasini E, Pastrello C, Rahmati S, Angeli M, Kotlyar M, Ghanekar A, Jurisica I

Case Control Study

- 109 Association of interferon lambda-4 rs12979860 polymorphism with hepatocellular carcinoma in patients with chronic hepatitis C infection
de Bitencorte JT, Rech TF, Lunge VR, dos Santos DC, Álvares-da-Silva MR, Simon D

Retrospective Study

- 120 Immunization status and hospitalization for vaccine-preventable and non-vaccine-preventable infections in liver-transplanted children
Sintusek P, Poovorawan Y

Observational Study

- 132 Endoscopic retrograde cholangiopancreatography and liver biopsy in the evaluation of elevated liver function tests after liver transplantation
Attwell A, Han S, Kriss M

META-ANALYSIS

- 144** Effectiveness of entecavir in preventing hepatocellular carcinoma development is genotype-dependent in hepatitis B virus-associated liver cirrhosis

Tarao K, Nozaki A, Chuma M, Taguri M, Maeda S

CASE REPORT

- 151** Living-donor liver transplantation in Budd-Chiari syndrome with inferior vena cava complete thrombosis: A case report and review of the literature

Rocha-Santos V, Waisberg DR, Pinheiro RS, Nacif LS, Arantes RM, Ducatti L, Martino RB, Haddad LB, Galvao FH, Andraus W, Carneiro-D'Albuquerque LA

ABOUT COVER

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WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

INDEXING/ABSTRACTING

The *WJH* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database. The *WJH*'s CiteScore for 2019 is 5.8 and Scopus CiteScore rank 2019: Hepatology is 22/61.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Li-Li Wang; Production Department Director: Xiang Li; Editorial Office Director: Xiang Li.

NAME OF JOURNAL

World Journal of Hepatology

ISSN

ISSN 1948-5182 (online)

LAUNCH DATE

October 31, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Nikolaos Pyrsopoulos, Ke-Qin Hu, Koo Jeong Kang

EDITORIAL BOARD MEMBERS

<https://www.wjnet.com/1948-5182/editorialboard.htm>

PUBLICATION DATE

January 27, 2021

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INSTRUCTIONS TO AUTHORS

<https://www.wjnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Autophagy in liver diseases

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Conflict-of-interest statement: The authors declare that there are no conflicts of interest relevant to this article and no financial support.

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Abstract

Autophagy is the liver cell energy recycling system regulating a variety of homeostatic mechanisms. Damaged organelles, lipids and proteins are degraded in the lysosomes and their elements are re-used by the cell. Investigations on autophagy have led to the award of two Nobel Prizes and a health of important reports. In this review we describe the fundamental functions of autophagy in the liver including new data on the regulation of autophagy. Moreover we emphasize the fact that autophagy acts like a two edge sword in many occasions with the most prominent paradigm being its involvement in the initiation and progress of hepatocellular carcinoma. We also focused to the implication of autophagy and its specialized forms of lipophagy and mitophagy in the pathogenesis of various liver diseases. We analyzed autophagy not only in well studied diseases, like alcoholic and nonalcoholic fatty liver and liver fibrosis but also in viral hepatitis, biliary diseases, autoimmune hepatitis and rare diseases including inherited metabolic diseases and also acetaminophene hepatotoxicity. We also stressed the different consequences that activation or impairment of autophagy may have in hepatocytes as opposed to Kupffer cells, sinusoidal endothelial cells or hepatic stellate cells. Finally, we analyzed the limited clinical data compared to the extensive experimental evidence and the possible future therapeutic interventions based on autophagy manipulation.

Key Words: Autophagy; Lipophagy; Mitophagy; Fatty liver disease; Fibrosis; Liver sinusoidal cells

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Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Greece

Peer-review report's scientific quality classification

Grade A (Excellent): A

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

Received: July 9, 2020

Peer-review started: July 9, 2020

First decision: October 6, 2020

Revised: December 10, 2020

Accepted: December 26, 2020

Article in press: December 26, 2020

Published online: January 27, 2021

P-Reviewer: Pan Q, Tavernarakis N

S-Editor: Gao CC

L-Editor: A

P-Editor: Wang LL



Core Tip: Extensive investigation of autophagy is mostly based on experimental data. However there is now enough evidence to support the notion that autophagy is not only the waste recycling mechanism of the hepatocyte, but is strongly involved in the pathogenesis of almost all liver diseases. It can be either a defensive mechanism against various insults or a detrimental machinery aggravating the underlying disease. Modulation of autophagy has different consequences in the hepatocyte than in the liver macrophages, the sinusoidal endothelium or the hepatic stellate cells. There is also an opportunity for future treatment applications of autophagy manipulation.

Citation: Kouroumalis E, Voumvouraki A, Augoustaki A, Samonakis DN. Autophagy in liver diseases. *World J Hepatol* 2021; 13(1): 6-65

URL: <https://www.wjgnet.com/1948-5182/full/v13/i1/6.htm>

DOI: <https://dx.doi.org/10.4254/wjh.v13.i1.6>

INTRODUCTION

Autophagy in the liver

Autophagy (from the Greek self-eating) is a process crucial for cell survival^[1,2]. Autophagy is a lysosomal degradation pathway that controls the disposition of intracellular waste including damaged organelles or invading pathogens. It can be characterized as the recycling energy system of the cell.

Under basal conditions autophagy degrades 1.5% of total hepatic protein per hour but in starvation, protein degradation increases to 4.5% of liver protein per hour^[3]. When rodents are starved for 48 h, autophagy degrades up to 40% of liver protein^[4].

Although It is accepted that the term “autophagy” was introduced in 1963 by the Belgian researcher Christian René de Duve, in fact the term autophagy was used almost a century earlier by Anselmier in a French journal^[5].

However the modern era of autophagy started with the pioneer work of de Duve and Novicoff in the 1950s when acid phosphatase positive lysosomes were described in the rat liver^[6-9] and the term lysosome was used for the first time^[10]. Later de Duve introduced the term autophagosome and Arstila and Trump proved that the autophagosomes originate from the endoplasmic reticulum (ER)^[11]. The next important progress came when Takeshige *et al*^[12] identified approximately fifteen Autophagy related genes (Atgs) involved in *Saccharomyces cerevisiae* autophagy^[12-14]. Today, more than 40 Atgs in various animal and human cells have been identified and unified^[15-17]. The importance of autophagy was recognized by the award of two Nobel Prizes for Physiology or Medicine, the first to Cristian De Duve in 1974 and the second to Yoshinori Ohsumi in 2016^[18,19]. Landmarks of autophagy were recently described^[20]. During the period 2008-2018 more than 33000 papers related to autophagy were published^[21,22].

Autophagy has certain discrete stages including induction, phagophore formation, autophagosome formation, autolysosome formation and degradation^[23-25]. Atg molecules are involved in various complexes essential for autophagy induction and autophagosome formation^[26]. Initiation starts with activation of the unc-51-like kinase 1 complex (ULK1, Atg1 in yeast) followed by beclin 1 (Atg6 in yeast) and a subsequent cascade of Atg proteins leading to autophagosome formation where LC3 (Atg8 in yeast) is implicated^[27]. LC3 is further processed to form initially LC3-I and then LC3-II^[28]. Once the autophagosome is formed, a blockage of autophagic flux at late steps will downregulate the clearance of autophagosomes. A blockage of autophagic flux finally results in autophagy dependent cell death^[29]. Detailed descriptions of the complex molecular steps of each stage of autophagy were recently published^[20,28,30].

A commonly used marker for estimating autophagosome formation is the fusion protein green fluorescent protein-LC3 (GFP-LC3)^[31]. Of the three members LC3A, LC3B, and LC3C of the human LC3 gene family, LC3B and LC3-II are mostly used for autophagy assays^[32-34]. Autophagic flux into the lysosomes is estimated by measuring p62/SQSTM1 degradation. p62/SQSTM1 is a protein complex that binds to LC3 and is efficiently degraded by autophagy^[35]. The total cellular level of p62/SQSTM1 inversely correlates with autophagic activity. Thus in autophagy-deficient cells, p62/SQSTM1 levels are increased after starvation in contrast to cells with normal autophagy^[36].

It should be stressed that the level of LC3 is related to the induction of autophagy

but might not reflect the final stages of autophagy and should not be used as a general marker of autophagy^[34-36]. Further progress of autophagy is detected by a low level of p62 since p62 degradation depends on the function of the autophagosome-lysosome fusion^[37]. Therefore an increase of both LC3 and p62 indicates formation of autophagosomes without lysosomal degradation^[38].

As mentioned before, a major breakthrough in autophagy was the identification of Atgs. Evidence for the importance of autophagy in liver homeostasis was provided by the generation of Atgs-knockout mice models^[39]. Livers of mice with deletion of the autophagy gene Atg7 were markedly enlarged, up to 30% of the body weight of the animal and hepatocytes were characterized by structural alterations of mitochondria and peroxisomes and aggregation of ubiquitinated proteins. These aggregates disappeared when the ATg7- knockout mouse was bred to a mouse null for SQSTM1/p62 indicating that SQSTM1 is important to direct damaged cytosolic proteins into the autophagic pathway^[40,41].

To date, three major types of autophagy, namely, macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA), have been described^[22,42,43].

Macroautophagy is the classical pathway that engulfs the cytosolic components targeted for lysosomal degradation. Initiation of autophagy is controlled by two metabolic sensors the mammalian target of rapamycin complex 1 (mTORC1) and the AMP-activated protein kinase (AMPK). mTORC1 negatively regulates autophagy by direct phosphorylation of ULK1 thus inhibiting ULK1. AMPK suppresses mTORC1 activity by phosphorylation of tuberous sclerosis 2 and raptor, two essential regulators of mTORC1^[44,45]. Recently it was reported that the final step in this activation process of mTOR is dependent on Rheb, a small GTPase that binds to mTOR and allosterically activates its kinase activity^[46]. The long-term regulation of autophagy is carried out by transcription factor EB (TFEB)^[47], the main regulator of lysosomal biogenesis and autophagy. Under nutrient-rich conditions, mTORC1 phosphorylates TFEB and retains TFEB in the cytosol^[48-50]. Nutrient deprivation on the other hand leads to mTORC1 inhibition, dephosphorylation of TFEB and its translocation to the nucleus to initiate the rapid transcription of autophagy genes^[51,52]. All subsequent series of complex events leading to the final degradation in lysosomes have elegantly been described^[2,24,53].

A simplified scheme of macroautophagy is presented in **Figure 1**.

Microautophagy is the least studied type of autophagy where compounds or membranous vesicles are directly taken up by lysosomes^[54]. Microautophagy is important during amino acid starvation^[55,56] and possibly three different types can be recognized^[57].

Chaperone Mediated Autophagy (CMA) is a selective engulfment process of substrates containing the pentapeptide “Lys-Phe-Glu-Arg-Gln” (KFERQ) motifs. They are recognized by, the cytosolic chaperone heat-shock cognate protein of 70 kDa (HSC70), and transported into the lysosomes through the lysosomal membrane protein 2A (LAMP2A)^[58,59]. CMA is induced by DNA damage, hypoxia and oxidative stress, among others^[60-65].

Today macroautophagy is also divided into non selective autophagy and selective macroautophagy targeting special organelles or specific compounds for degradation^[43,66,67]. Thus new names have appeared according to the compounds involved: Ribophagy (ribosomes)^[68], pexophagy (peroxisomes)^[69], ferritinophagy (iron-based compounds)^[70] and most importantly reticulophagy (ER)^[71] lipophagy (lipids)^[72] and mitophagy (mitochondria)^[73]. The last two are practically involved in every form of fatty liver.

Reticulophagy: Multiple receptors directly interact with LC3 and form autophagosomes during reticulophagy, a very important form of macroautophagy that preserves the size and function of the ER in different conditions like starvation, non-alcoholic fatty liver disease (NAFLD), viral infections and fibrosis^[74-79].

Lipophagy: Lipophagy is implicated in lipid homeostasis and metabolism in liver diseases. It is usually down-regulated in steatosis of either alcoholic or non-alcoholic liver disease^[80-84], but it is up-regulated when fibrosis, cirrhosis or hepatocellular carcinoma are evolving^[85-87]. Comprehensive reviews of lipophagy in liver disease were recently presented^[88-91].

Mitophagy: The first step of mitophagy in mammals requires the induction of canonic Atg-dependent autophagy with either mTOR suppression induced by mitochondrial generated reactive oxygen species (ROS), or AMPK activation induced by adenosine triphosphate (ATP) depletion. The second step is the priming of the mitochondria involving molecular modifications leading to their recognition by the autophagy

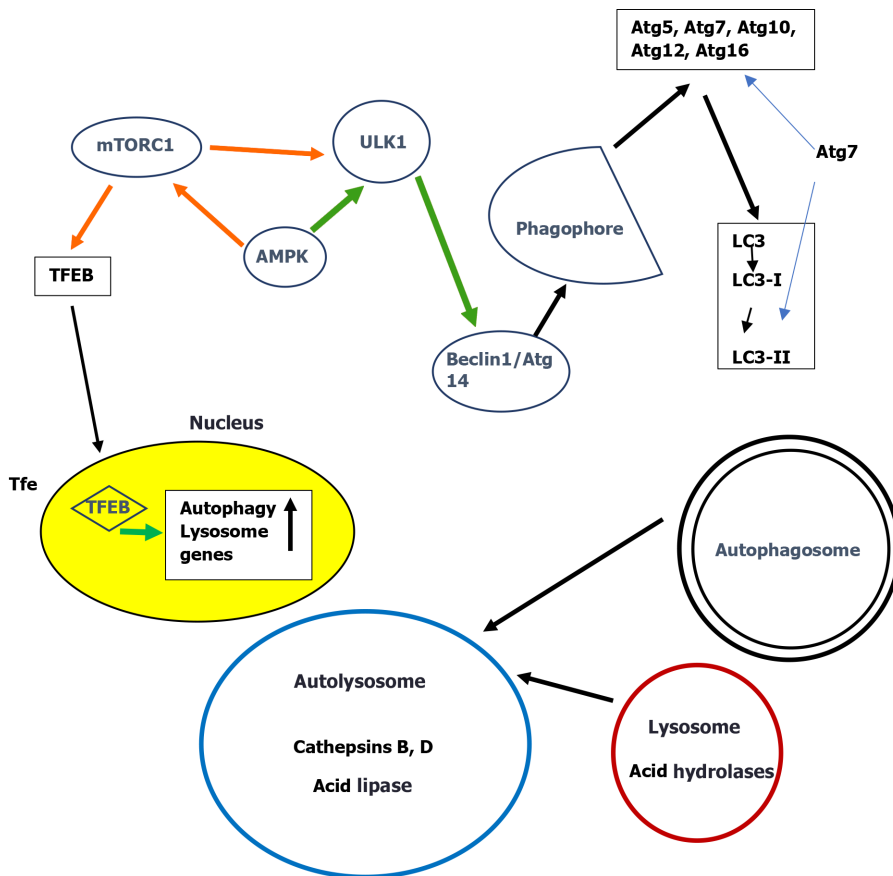


Figure 1 A simplified scheme of the macroautophagy pathways in the liver. Initiation starts with activation of the unc-51-like kinase 1 complex (ULK1, Atg1 in yeast) followed by beclin 1 (Atg6 in yeast) and a subsequent cascade of Atg proteins leading to autophagosome formation where LC3 (Atg8 in yeast) is implicated. LC3 is further processed to form initially LC3-I and then LC3-II. Fusion of the autophagosomes with lysosomes form the autolysosome where acid proteases (among which cathepsins are important) and lipases degrade proteins and lipids. Initiation of autophagy is controlled by two metabolic sensors the mammalian target of rapamycin complex 1 (mTORC1) and the AMP-activated protein kinase (AMPK). mTORC1 negatively regulates autophagy inhibiting ULK1. AMPK suppresses mTORC1 activity. The long-term regulation of autophagy is carried out by transcription factor EB (TFEB), the main regulator of lysosomal biogenesis and autophagy. Under nutrient-rich conditions, mTORC1 phosphorylates TFEB and retains TFEB in the cytosol. Orange arrows: Inhibition. Green arrows: Positive regulation. For details see Ref.^[21,29,31]. mTORC1: Mammalian target of rapamycin complex 1; TFEB: Transcription factor EB; ULK1: Unc-51-like kinase 1 complex.

gosomes^[92,93]. Even in the healthy liver, worn out mitochondria with a half-life of 10 to 25 d are removed by mitophagy^[94,95]. Elimination of aged or damaged mitochondria protect cells from release of pro-apoptotic proteins, generation of toxic ROS and non proper hydrolysis of ATP^[96-99]. When oxidative stress appears, autophagy rapidly acts to remove oxidized proteins or damaged mitochondria that generate more ROS. Recent data show that in autophagy deficiency there is accumulation of ROS and p62 probably mediated by the loss of FOXO1/3. It has been reported that the p62-FOXO1/3 axis is the molecular basis for the reduction of antioxidant defense in autophagy deficiency^[100]. Three different types of mitophagy have been described based in the different molecular pathways involved^[101,102]. An extensive review of molecular mechanisms of mitophagy in liver diseases has been recently published^[103].

New players in liver autophagy: It is clear today that apart from the known pathways regulating liver autophagy, there are additional mechanisms involved. The most important are the long non-coding RNAs (lncRNAs), microRNAs (miRNAs) and exosomes. Many recent studies have presented strong evidence that ncRNAs influence autophagy by regulating various autophagy pathways^[104-110]. Equally, miRNAs regulate autophagy influencing the core autophagy pathways^[111].

Evidence from experimental animals with liver specific deletions of Atgs has demonstrated the role of High mobility group box 1 (HMGB1)^[112] and Yes-associated protein (YAP)^[113] in the pathological changes induced by autophagy. Nuclear receptors were also reported to control autophagy. Activation of the farnesoid X receptor (FXR), occurs during feeding and suppresses Atgs expression. On the other hand during starvation, fasting-activated nuclear receptors, the peroxisome proliferator-activated

receptor alpha (PPAR), and the cAMP response element-binding protein (CREB), induce expression of Atgs and therefore increase autophagy^[114-116].

An association of autophagy with the formation and function of exosomes has also been described. Exosomes are extracellular vesicles originating from late endosomes, which do not fuse with lysosomes but are released extracellularly by exocytosis. Exosomes can either activate autophagy pathways or transfer extracellular vesicles to the lysosomes^[117]. The interplay between autophagy and exosome biogenesis has been recently described^[118].

Most researchers have studied either the early or the late stages of autophagy. However equally important is the final stage, namely the lysosome reformation (ALR), leading to regeneration of functional lysosomes from autolysosomes. A series of proteins including clathrin, the motor protein KIF5B, and dynamin 2 are sequentially involved up to the maturation of functional lysosomes. Early lysosomes are pH-neutral but eventually they gain acidity and luminal proteins^[119-122]. Accumulating evidence suggests that most, if not all, components of the molecular machinery for autophagy also mediate autophagy-independent functions. Autophagy is involved in various cell functions like endocytosis, phagocytosis, DNA repair, centrosome function, cell proliferation, cell death and immunological response including memory. Details were recently reported^[123].

Autophagy and immunity: The implication of autophagy with the immune system has been investigated in the last few years^[124-131]. Non-canonical forms of macroautophagy were described, resulting in the formation of autophagosomes that fuse with the lysosomes^[132]. Only a subset of the Atgs machinery is used. Among these, LC3-associated phagocytosis (LAP) has been extensively studied because of its implication in immune regulation. LAP recruits LC3-II to the phagosomal membrane^[133-135] and is taken up by macrophages through innate immune receptors such as Toll-like receptors. In contrast to autophagy the LAPosome is a single membrane vacuole. In contrast to autophagy, ULK1 is not required for LAP^[133]. Chaperone-mediated autophagy has also attracted attention because of its central role in antigen presentation and aging^[136,137]. Autophagy is also implicated in the function of innate immunity interfering with macrophage autophagy. There is interplay between autophagy and innate immunity as interferon (IFN)- γ promotes autophagy in macrophages^[138]. Mice fed with high fat diet had impaired autophagy in bone marrow-derived macrophages and peritoneal macrophages^[139]. Mice with Atg5 deficient macrophages, developed hepatic inflammation when stimulated with lipopolysaccharide (LPS) after a high fat diet feeding. Acquired immunity is primarily a defense function against specific pathogens and is brought about by the different subsets of T cells and B cells. Interestingly there is evidence that high autophagic activity maintains the differentiation and function of important T-cell subsets such as regulatory T (Treg)-cells^[140] and $\gamma \delta$ T-cells^[141].

Autophagy and cell death: It has been proven that autophagy can be either a protective mechanism or a contributor to cellular death in certain instances^[142-144]. Autophagy is involved in cellular death mostly by its effects on apoptosis. Autophagy is connected to apoptosis and these two cellular destructive phenomena are affecting each other^[145-148]. This is particularly important in hepatic cell death^[149].

Generally autophagy blocks the induction of caspase-dependent apoptosis, and apoptosis-associated caspase activation stops the autophagic process. Yet, in special cases, autophagy may induce apoptosis or necrosis, and autophagy has been shown to degrade the cytoplasm, leading to 'autophagic cell death'^[150-152].

Autophagy is also implicated in caspase-independent cell death, leading to necrosis and necroptosis^[153]. Induction of apoptosis eliminates cells damaged through the action of the tumor suppressor gene p53^[154]. Apoptosis is counteracted, among others, by the mTOR/AKT pathway also involved in autophagy. The balance between p53 and AKT/mTOR is crucial for the fate of injured cells^[155,156]. In addition, autophagy induces a particular mechanism of cell death named ferroptosis. It was initially reported as a specific iron-dependent form of malignant cell death. It soon became clear that ferroptosis is a more general form of cell death^[157,158]. Many proteins implicated in autophagy (like Atgs and BECN1) were also involved in ferroptosis. Moreover activators of ferroptosis, like erastin, induced autophagosome accumulation and activation of autophagy led to ferroptotic cell death possibly by the turnover of ferritin through ferritinophagy^[159-161].

A recent study has shown that ferroptosis is also interconnected with lipophagy. Lipids released during lipophagy and subsequent peroxidized increase ferroptosis. Therefore it might be that ferroptosis is a mechanism of cellular death in NAFLD^[162].

Autophagy and inflammation: Autophagy is also closely associated with the inflammatory response in the liver. Inflammasome and autophagy regulate each other by the same inhibitory mechanisms which however are controlled by different input pathways. The NLRP3 inflammasome activation, usually through the stimulation by pathogen- and/or danger-associated molecular patterns^[163,164], induces procaspase-1 activation which promotes interleukin (IL)-1 β and IL-18 production leading to pyroptotic cell death. These events are counteracted by caspase-1-mediated activation of autophagy. In addition autophagy reduces inflammasome activation degrading the inflammasomes in the autophagosomes but also eliminating damaged cytoplasmic organelles that otherwise would produce DAMPS increasing activation of inflammasomes^[165,166].

On the other hand, the negative correlation between inflammasomes and autophagy^[167-169] leads to an increased production of the pro-inflammatory IL-1 β ^[170] when autophagy is decreased^[128]. However, the relationship between NLRP3 and autophagy has not been fully clarified, and recent studies have reported that nuclear factor-kappa beta (NF- κ B) activation can modulate the NLRP3 and autophagy towards the same direction^[171].

In view of the above is not surprising that many reviews on autophagy use the term “double-edged sword” stressing the fact that autophagy may have opposite effects on the same biological phenomenon^[172]. Prominent general paradigms are cancer^[173,174] and viral infections^[175].

Another characterization pertinent to the liver is that autophagy behaves like Jekyll and Hyde depending on the cells involved. In hepatocytes, macroautophagy [in NAFLD and alcoholic liver disease (ALD)] and CMA (in NAFLD) is protective. It reduces fat accumulation and oxidative stress, it removes damaged mitochondria and favors regeneration. In macrophages, macroautophagy inhibits liver inflammation and fibrosis but it enhances fibrosis activated stellate cells. It is protective in early phases of hepatocellular carcinoma, but may be detrimental in late phases^[176,177].

Autophagy in hepatocytes but also in the non-parenchymal sinusoidal cells of the liver is a key for liver physiology^[178,179] and defects of autophagy are implicated in the pathophysiology of most liver diseases^[180]. Both common diseases like alcoholic and non-alcoholic fatty liver or viral hepatitis and rare entities like Wilson’s disease and α 1 antitrypsin deficiency are related to autophagy defects^[30,41,57,181-184]. Defective autophagy also leads to accumulation of detrimental hepatocyte byproducts due to the fact that hepatocytes have a long half life of 6-12 mo^[143]. Moreover, the liver is responsible for handling of a large number of xenobiotics and autophagy is a cytoprotective mechanism^[99,185] (Figure 2).

OBESITY, STEATOSIS AND NAFLD

NAFLD is the commonest liver disease worldwide. Recently it was suggested that it should be renamed as metabolic dysfunction-associated fatty liver disease (MAFLD)^[186,187]. Pathological lesions in the liver vary from simple steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis. Current pathogenesis of NASH is mainly focused on the effects of insulin resistance and lipotoxicity in hepatocytes^[188]. The abnormalities reported in Kupffer cells, stellate cells and endothelial cells are regarded as secondary events^[189,190].

Obesity and insulin resistance are well documented risk factors for NAFLD development. Defects in liver autophagy have been established as fundamental abnormalities in both conditions.

Hepatic autophagy in obesity and insulin resistance

In the hepatocyte, lipids are catabolized by two major pathways. The first involves cytoplasmic neutral lipases and the second is lipophagy and acid lipases and hydrolases of the lysosomes. The end result is the production of free fatty acids that are further broken down by β I-oxidase in the mitochondria^[191].

Lipid droplets have a core of lipids enwrapped in a phospholipid layer characterized by proteins called perilipins directing them to the autophagosome^[72]. A crucial protein mediating lipolysis and autophagy is the adipose triglyceride lipase (ATGL). Cytoplasmic lipolysis and lipophagy are interconnected. The degradation of perilipins by autophagy facilitates actions of ATGL which in turn induces autophagy *via* sirtuin1 deacetylation of certain Atgs and activation of the transcription factors FoxO1 and FoxO3 thus promoting autophagy^[192-194].

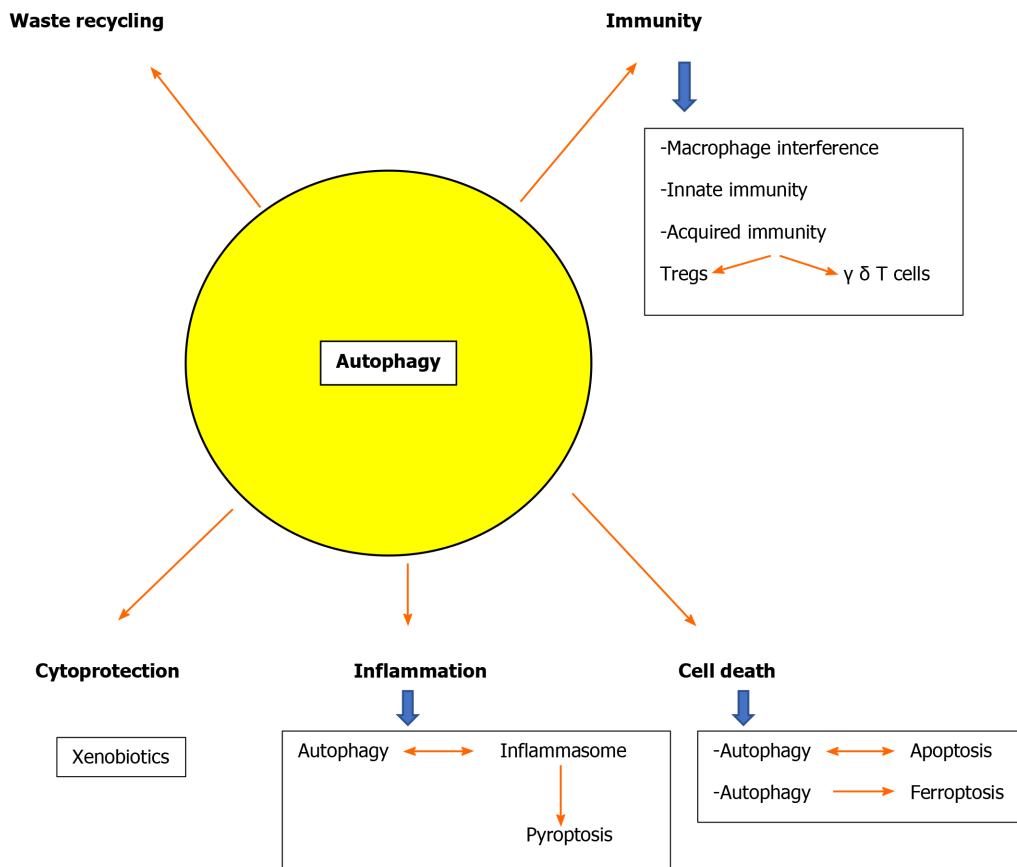


Figure 2 Implications of autophagy in critical cellular functions in the liver. For details see text.

Lipophagy can prevent lipid accumulation in hepatocytes, while the inhibition of lipophagy promotes lipid droplets (LDs) accumulation, resulting in hepatocellular steatosis^[195].

Characteristic changes of the metabolic syndrome like obesity, hyperglycemia, and dyslipidemia have been shown to exert a negative effect on autophagy because the regulatory control of forkhead box O1 (FoxO1) on the expression of *Atg* genes is lost leading to autophagy malfunction^[196]. Macroautophagy and CMA are also down-regulated by increased intracellular lipids due to either interference with the lysosomal stability of the CMA receptor or to the reduction of the ability of autophagosomes to fuse with lysosomes leading to the reduction of macroautophagic flux^[196-198].

The severity of steatosis is related to the expression of three proteins, the damage regulated autophagy modulator (DRAM), BAX and p53. In mice livers, p53 expression increased in mild and severe steatosis. A DRAM expression increase was observed in mild hepatosteatosis, whereas high BAX expression was identified in severe hepatosteatosis^[199].

A clinical study has confirmed the link between induction of autophagy and liver steatosis^[200]. Autophagy-related genes (*Atg5*, *LC3A*, and *LC3B*) were overexpressed in obese patients compared with non obese patients.

Experimental evidence also suggests that defective autophagy is crucial in the development of obesity, oxidative stress, and the metabolic syndrome^[201-203].

Insulin is intimately involved in autophagy regulation as the mTOR inhibitor of the FoxO and TFEB controllers of the transcription of autophagic genes is insulin-inducible^[204]. Overactivation of mTOR in turn leads to insulin resistance^[205,206]. Several mechanisms might explain this defect in obesity. Obesity increases calpain-2 by a still unknown signal pathway. Calpain is a protease that degrades *Atg7* and modulates autophagy^[201]. Autophagosome-lysosome fusion is also defective in livers of obese mice due to alterations of the lipids in cellular membranes induced by the high-fat diet^[198]. A defective liver autophagy and the associated decrease of lysosomal degradation contribute to an additional increase in the ER stress which leads to insulin resistance and a vicious circle is completed^[201,207,208]. Hyper-insulinemia decreases liver autophagy and reduced hepatic autophagy aggravates ER stress and insulin resistance.

An additional mechanism is a defect in acidification of lysosomes. Impaired substrate degradation in autolysosomes has also been reported for obese ob/ob mice. Activities of lysosomal cathepsins were implicated in obesity. Cathepsin L was decreased in obese adipose tissue, while Cathepsin B was significantly elevated. Interestingly in obese adipose tissue inflammasomes were activated and further upregulation of cathepsin B resulted in additional activation of inflammasomes^[209-212].

A study of the expression of 322 lysosomal/autophagic genes was recently reported in adipose tissue of lean and obese patients. Among 35 significantly expressed genes, 34 were upregulated. In isolated murine cells, tumor necrosis factor alpha (TNF α) stimulation resulted in upregulation of lysosomal/autophagic genes accompanied by upregulation of the autophagy associated SQSTM1/p62 receptor leading to increased degradation of perilipin 1. It seems that local inflammatory cytokines may impair lipid storage *via* autophagy induction^[213].

An extensive review of lysosomal enzyme abnormalities in both adipose and liver tissue was recently published^[214]. A recent report suggests an additional mechanism contributing to obesity-associated abnormalities. Obesity increases lysosomal iNOS and NO production leading to exacerbation of lysosomal nitrosative stress, impairment of lysosomal function, defective autophagy and insulin resistance^[215].

There is also evidence that mitophagy is negatively regulated by liver insulin resistance. Mitophagy can promote mitochondrial fatty acid oxidation to inhibit hepatic fatty acid accumulation and improve hepatic insulin resistance. Fundc1 is a recently characterized mitophagy receptor and mice lacking this receptor develop severe obesity and insulin resistance when maintained in a high-fat diet^[216,217].

However, when autophagy is defective an alternative mechanism protects the liver from steatosis. An induction of fibroblast growth factor 21 (FGF21) was reported in mice with subsequent amelioration of insulin resistance and decreased diet-induced obesity^[218,219]. This has been corroborated in a clinical study of overweight NAFLD patients, where increased FGF21 levels were correlated with steatosis grade, fibrosis and lobular inflammation. NASH patients had the highest levels^[220]. An analogue of FGF21 has been tested in experimental animals and obese diabetic patients with promising results^[221-223]. Nevertheless, the control of adipose tissue biology is very complex and is elegantly described in a recent publication^[224].

NAFLD-NASH

Not surprisingly autophagy is strongly associated with NAFLD pathogenesis^[179]. Diet-induced NAFLD in mice blocks hepatic autophagy and leads to oxidative stress and mitochondrial dysfunction^[225], also reducing thyroid hormone-induced mitophagy^[226]. The potential molecular pathways and possible therapeutic implications of thyroid hormones in NAFLD have been recently reviewed^[227].

Mitophagy abnormalities are strongly implicated in NAFLD^[228-230]. In particular an impairment of mitophagy seems to activate the NLRP3 inflammasome favoring the progression of NAFLD to NASH^[38]. Accordingly, recent evidence indicates that restoration of mitophagy may improve NAFLD^[231-234].

In addition to mitophagy, reticulophagy is also implicated in NAFLD. An extensive reticulophagic response is evident in hepatocytes after induction of NAFLD by oleic acid^[228,235]. It is suggested that reticulophagy and mitophagy are independent, events involved in NAFLD progression^[228].

Impaired lipophagy and lipotoxicity are also strongly involved in NAFLD^[72,192,236,237]. Lipid accumulation in hepatocytes blocks autophagic flux and impaired autophagic flux favors the progress of NAFLD^[30].

This impaired flux and the subsequent ER stress can be improved by inhibition of the sterol regulatory element-binding protein 2 (SREBP-2) whose activation promotes accumulation of cholesterol in NAFLD. This improvement is associated with upregulation of autophagy genes^[238].

Intracellular lipid trafficking is also regulated by store operated calcium entry and enhanced lipophagy is observed in cells defective in this system^[239]. Moreover, the detrimental effects of diets rich in saturated FFA were increased by siRNA-3, which enhanced lipotoxicity, reducing the autophagic flux^[240]. The effect of lipophagy in liver steatosis is further supported by experimental evidence that various chemicals are involved in steatosis by interfering with autophagy. Caffeine reduces lipid content and stimulates beta-oxidation in hepatocytes through autophagy in mammalian liver cells in NAFLD^[17]. In essence caffeine protects against fatty liver through the co-ordination of the induced lipophagy and mitochondrial β -oxidation^[241,242]. Epidemiologic studies

demonstrated that coffee consumption reduced the development of fatty liver, fibrosis, and hepatocellular carcinoma in NAFLD patients^[243,244] supporting thus the experimental evidence.

Methionine is a well known inactivator of autophagy and lipophagy. The correlation between lipophagy and methionine in the liver from patients with liver steatosis has been studied. Increased levels of methionine inhibit autophagic catabolism of lipids and contribute to liver steatosis in NAFLD^[83]. Mice fed with a methionine/choline deficient diet developed steatosis, inflammation, fibrosis and ER stress associated with mitochondrial dysfunction. The administration of the autophagy enhancer rapamycin ameliorated these lesions while chloroquine, a well established autophagy inhibitor, aggravated the liver injury^[245]. Resveratrol, another autophagy activator, also attenuated liver lesions induced by a similar diet^[246,247]. Consistent with these findings is a recent report that a traditional Chinese herb increased autophagy and considerably improved steatohepatitis induced by methionine/choline deficient diet in rats^[248].

Other diet-supplied molecules affect autophagy and are possibly beneficial in NAFLD including the purple sweet potato color^[249]. Likewise, the caffeic acid of vegetables has been reported to ameliorate hepatic steatosis^[250] while curcumin, an antioxidant polyphenol of *Curcuma longa*, has been shown to inhibit apoptosis and induce autophagy with a potential protective effect on hepatocellular carcinoma^[251].

A finding that might be useful in future treatment of NAFLD was recently reported. Celecoxib, a COX-2 inhibitor, attenuated steatosis and restored autophagic flux in cells treated with palmitate and rats fed a high fat diet^[252].

Other lipids like the sphingolipid ceramide may be implicated in NAFLD as it is increased in Atg7 knockout mouse liver in parallel with the impaired autophagy^[253]. Autophagy increased when sphingolipid de novo synthesis was upregulated, indicating that lipid degradation was activated to prevent excessive sphingolipid accumulation.

Interestingly, autophagic activity seems to be upregulated when the renin angiotensin system is overexpressed. The underlying mechanisms and its role in NAFLD have yet to be clarified as there are many controversial issues to be solved^[254]. Overall there is extensive evidence that inhibition of lipophagy is detrimental for the liver in NAFLD^[198,222,238,255].

Summarizing the above studies, a therapeutic approach against NAFLD would be the activation of lipophagy^[90]. However, it is noteworthy that there is one study indicating the opposite, as suppression of autophagy through inhibition of c-Jun N-terminal Kinase (JNK) ameliorates insulin resistance in a rat NAFLD model^[256].

Extensive reviews on the mechanisms of autophagy deregulation in NAFLD were recently published^[183,257,258]. Not only impaired macroautophagy but also reduced liver chaperon mediated autophagy (CMA) favors steatosis due to failure in the timely removal of perilipins^[259,260] and therefore an increase in lipogenic enzymes. When oxidative stress is increased in the liver, an upregulation of CMA occurs to selectively remove damaged proteins^[62]. Loss of CMA leads to impairment of proteostasis and accumulation of oxidized protein aggregates perpetuating thus chronic oxidative stress^[261].

Autophagy and NASH

Involvement of autophagy in the progression of NAFLD to NASH has not yet been clarified and molecular mechanisms are not fully understood.

One of the histological characteristics of NASH used in diagnosis and scoring systems is the formation of Mallory-Denk bodies (MDB)^[262-264]. There is experimental evidence that inhibition of autophagy and accumulation of p62 is related to their formation while autophagy activation with rapamycin leads to their resolution^[265]. Further support of the involvement of autophagy in NAFLD evolution to NASH was reported in a clinical and experimental study where a decrease of autophagic flux in parallel with an increase in ER stress was demonstrated both in the livers from NAFLD patients and mice models of NAFLD, and in lipid-overloaded human hepatocytes^[266]. However tests for measurements of autophagic flux used in this paper are not full-proof as they can be influenced by autophagy independent factors. Therefore these findings should be corroborated in a different set up.

Patients with NASH and murine models of steatotic inflammation had reduced expression of Atg7 and TFEB while the autophagy inhibitor rubicon was increased^[139,177,255].

In contrast, steatosis and liver injury were improved in parallel with restoration of autophagy and reduction of ER stress in mice with a deletion of the Rubicon or adenoviral delivery of Atg7^[202,251]. Recent evidence also indicates that impaired

mitophagy may contribute to liver injury during progression of NAFLD and formation of megamitochondria^[229].

Transition of NAFLD to NASH also implicates Kupffer cells. These cells, constitute 80%-90% of tissue macrophages in the body and are critical cells in liver inflammation^[20]. They are the main site of NLRP3 inflammasome activation and production of the pro-inflammatory cytokines compared to hepatocytes and stellate cells^[267,268]. Activation of the NLRP3 inflammasome plays an important role in the transition from NAFLD to NASH^[269].

An earlier report demonstrated that cathepsin B, a lysosomal cysteine protease, is released in the cytosol in response to FFAs and that this redistribution of cathepsin B is present in the liver of patients with NAFLD related to disease severity. Importantly in a dietary mouse model of NAFLD, inhibition of Cath B significantly decreased steatosis, liver inflammation and insulin resistance^[270].

These findings were recently elaborated in more detail as it was reported that cathepsin B and activation of the NLRP3 inflammasome are interconnected in a murine model of NASH but also in isolated Kupffer cells stimulated with palmitate. Expression of cathepsin B and activation of NLRP3 inflammasome were increase in NASH animals. Moreover, an inhibition of Cathepsin B decreased liver inflammation, ballooning, and the pro-inflammatory cytokines IL-1 β and IL-18. *In vitro* stimulation of Kupffer cells showed identical results in inflammasome activation, expression of Cath.B and cytokine production before and after Cath.B inhibition. These results indicate that NASH pathogenesis probably depends in part to inflammasome activation which in turn is regulated by the activity of a protease tightly connected to autophagy^[271].

Additional supporting evidence for the role of autophagy in NASH pathogenesis is the fact that impaired autophagy in obese mice is critical for macrophage polarization. M2 macrophage polarization relies on energy provided by FFA oxidation, suggesting a potential implication of autophagy in this process. Macrophages change to a pro-inflammatory phenotype due to both increased M1 and decreased M2 polarization^[132] with a resultant upregulation of liver inflammation, a prominent feature of NASH.

The situation is controversial when adipose tissue macrophages from obese mice are concerned. Increased rather than decreased autophagy of macrophages has been demonstrated in adipose tissue^[272,273]. Another cathepsin mostly found in Kupffer cells seems to be implicated in NASH. Lysosomal cholesterol accumulation inside murine Kupffer cells leads to increased liver Cathepsin D activity which is related to liver inflammation^[274]. Kupffer cell cathepsin D may therefore be an additional key player in hepatic inflammation of NASH^[275]. The impairment of macrophage autophagy with aging may explain in part the increased prevalence of the metabolic syndrome and steatohepatitis of older age in humans^[276,277].

The oxidative stress is also involved in the progression to NASH. Hepatocytes exposed to palmitate concentrations similar to those found in patients with the metabolic syndrome and NAFLD showed mitochondrial membrane permeabilization and production of ROS. Similarly, an inhibition of Cathepsin B ameliorated mitochondrial dysfunction and oxidative stress, indicating an additional mechanism of NASH progression^[229,278].

Under normal conditions, damaged mitochondria are removed through mitophagy. In certain cases of NAFLD however mitophagy is defective and the oxidation of biomolecules by mitochondrial ROS starts a vicious cycle of increasing mitochondrial dysfunction and aggravation of hepatocellular oxidative damage. This ultimately leads to hepatic inflammation and liver failure^[279,280], since impaired mitophagy triggers liver NLRP3 inflammasome activation *in vivo* and *in vitro* in isolated murine hepatocytes^[38].

Impairment of autophagy in other liver sinusoidal cells may also participate in the progression of NAFLD to NASH. Decreased autophagy has been observed in the liver endothelial cells of patients with NASH or in mice with endothelial deletion of Atg5 and features of inflammation^[180,190,281]. A very recent study has convincingly shown that impaired autophagy of liver endothelial cells (LSECs) occurs in NASH patients but not in simple steatosis. Deficiency in autophagy in LSECs induces endothelial inflammation ultimately leading to liver inflammation and fibrosis. This defective autophagy, in part due to inflammatory mediators of the portal blood, might well be one of the missing links of the progression of simple steatosis to NASH and cirrhosis^[282].

A further mechanisms leading to NASH involves multivesicular bodies (MVBs), a form of endosomes, whose contents are transported into lysosomes^[283]. The MVB-lysosomal pathway was shown to participate in the development of steatohepatitis through lysosomal degradation of Toll-like receptor 4 reported to be critical for the progression of NASH^[284].

Finally a role of the chemokine CXCL10 in the development of steatohepatitis has been proposed. Upregulation of CXCL10 impairs autophagic flux decreasing thus autolysosome formation. Autophagic protein degradation is inhibited followed by the accumulation of ubiquitinated proteins with ultimate development of steatohepatitis^[285].

ALD

The liver is the organ mostly responsible for ethanol metabolism. Oxidation of ethanol happens through three pathways namely alcohol dehydrogenase in the cytosol, cytochrome P450 (CYP2E1) in the ER and microsomes and the enzyme catalase in peroxisomes^[286]. Ethanol oxidation also produces ROS, including superoxide anion, and hydroxyl radicals that may damage hepatocytes^[287].

Ethanol induces autophagosome formation in the liver. Reduction of autophagy results in the accumulation of lipid droplets and apoptosis of hepatocytes^[288]. On the other hand activation of autophagy by rapamycin attenuates steatosis and injury induced by a combination of ethanol and lipopolysaccharide^[289].

Induction of autophagy by acute ethanol exposure is mediated through many mechanisms. Ethanol-induced autophagy requires ethanol oxidation to acetaldehyde and ROS generation^[290,291]. ROS activates autophagy by suppressing mTOR and proteasome activity^[292,293] and inactivation of Atg4^[294].

Oxidants differentially influence the activities of the proteasome (the other major pathway of protein degradation.) Proteasomes are reduced when autophagosomes are increased^[295]. Proteasome inhibition further triggers ER stress activates autophagy through JNK activation. Ethanol may also suppress Akt and mTOR through the upregulation of PTEN^[296,297]. Metals, like zinc, are also implicated in autophagy alterations after ethanol treatment^[298].

A caution should be exercised on CYP2E1 ethanol oxidation as oxidative products resulting from the expression of CYP2E1 may in fact impair autophagy leading to lipid accumulation in the liver. In cells expressing CYP2E1, hepatocyte lipids and generation of ROS were increased by an inhibitor of autophagy and decreased when a stimulator of autophagy was used^[299]. Similar results were found after acute alcohol in CYP2E1 knockout mice^[291]. These findings also support the idea that autophagy protects against ethanol/CYP2E1-dependent hepatic injury.

It has also been shown that hepatic autophagy depends on the level of acetaldehyde produced during ethanol metabolism. Mice expressing the ALDH2 isoenzyme, clear acetaldehyde more rapidly and have increased autophagy and lower levels of hepatic triglycerides^[300]. Cannabinoid receptor 2 can also induce macrophage autophagy to protect from alcoholic liver damage^[301].

It should be stresses however that acute and chronic ethanol exposure may have different effects in liver autophagy^[302]. Increased autophagosome formation and autophagy flux were shown in cultured hepatocytes after short term incubation with ethanol or in livers of mice after acute alcohol administration^[288,302]. Enhanced autophagy parallel a higher hepatocyte nuclear content of TFEB, the main transcriptional regulator of genes involved in lysosome biogenesis^[49,50].

Alcohol also has an effect on the transcription factor forkhead box O3a (FoxO3a) that modulates liver autophagy^[303]. The activity of FoxO3a is largely controlled by multiple post-transcriptional modifications, including phosphorylation and acetylation^[304]. Acute ethanol exposure increases nuclear translocation of FoxO3a inducing its dephosphorylation and acetylation.

However, results are not uniform for the chronic ethanol effect. Chronic ethanol administration (Lieber-DeCarli model) for 4 wk or 10 wk increased autophagosome numbers in murine livers, suggesting the induction of autophagy^[305]. In another similar murine model, mice were given gradually increasing ethanol concentrations for 10 d and autophagic flux was reduced^[302].

The discrepancy seems to be solved by the report that autophagy response was dependent on the alcohol concentration used. In a murine model on Lieber-DeCarli diet with different levels of alcohol for 4 wk, autophagy is increased by a lower dose of alcohol (29% of the caloric need), but decreased by a higher dose (36% of the caloric need). Liver injury was aggravated by further reduction of autophagy and attenuated by autophagy activation^[306].

Earlier studies have also demonstrated that chronic alcohol exposure disrupts lysosome function^[307]. Overall results have demonstrated that autophagy is suppressed in chronic alcohol consumption due to either the defect of lysosomal function and

biogenesis from TFEB suppression^[302,308] or to a reduction in AMPK activity and inhibition of autophagosome formation^[309,310].

After ethanol-induced reduction of autophagy, there is accumulation of aggregated proteins and SQSTM1/p62, leading to activation of nuclear factor erythroid 2-related factor 2 (Nrf2) and damage to the mitochondria and cell death^[309,311].

How the other autophagy-related transcriptional factors, such as TFEB and farnesoid X receptor (FXR) are interconnected with FoxO3a in the expression of autophagy genes is unknown. Moreover, how ROS generation in acute or chronic alcoholic condition systematically affects the mTORC1 activation or TFEB translocation is unclear.

Autophagy is also protective against CYP2E1-dependent liver lesions in a chronically ethanol-fed murine model^[312]. Autophagy in ALD can be further affected by additional factors identified in various experimental models. Augmenter of liver regeneration (ALR) is a factor that can promote liver growth. It was reported to protect mice from ethanol-induced liver injury through inhibition of mTOR and therefore activation of autophagy^[313]. Moreover an interesting recent study used many genetic models of autophagy impairment, with different functional levels and different alcohol regimens. Deficiencies of either Atg7 or Atg5 demonstrated variable responses to ethanol feeding according to the timing of autophagy dysfunction, the gene being affected, and the alcohol scheme used^[314].

It should be stressed that in acute alcohol administration, ethanol-induced autophagy may protect the liver by three basic mechanisms namely mitophagy^[80,102,315,316], lipophagy^[72,293,317] and clearance of Mallory-Denk bodies by proteophagy^[265,318,319].

However, chronic alcohol exposure impairs autophagy and lipophagy^[308,320] most likely due to the activation of mTOR signaling and a decrease in lysosomal biogenesis. Administration of the mTOR inhibitor Torin-1 restores lysosomal biogenesis and attenuates liver lesions^[308]. An additional pathway through which chronic alcohol exposure could reduce liver autophagy is the inactivation of the guanosine triphosphate Rab7 and reduction of dynamin 2 activity leading to depletion of lysosomes and inhibition of hepatocyte lipophagy^[320,321].

Ethanol Induced steatosis activates mitophagy by elevating PINK1 expression on mitochondria^[305]. PINK1-dependent mitophagy was correlated with the mitochondrial expression of Parkin and the level of an indicator of oxidative mtDNA damage^[322-325]. Mitophagy has a dominant role in protection of the hepatocyte from alcohol-induced hepatic injury as evidenced by a report that enhancement of mitophagy by quercetin, a natural flavonoid, attenuated ethanol-induced mitochondrial damage^[326].

Regulation of mitophagy is related to three receptors namely FUN14 domain containing 1 (FUNDC1), BCL2 interacting protein 3 (Bnip3), and Parkin^[327].

DNA-dependent protein kinase catalytic subunit (DNA-PKcs) is a newly described housekeeper of liver mitochondrial fission. DNA-PKcs is overexpressed in murine livers after exposure to ethanol and was positively correlated with steatosis, mitochondrial damage and fibrosis. On the other hand this over expression repressed FUNDC1-required mitophagy^[328].

An additional significant point is the effect that ethanol might have on the different sinusoidal cell subpopulations. There is strong evidence that autophagy in macrophages is crucial to protect the liver from ethanol-induced damage. Investigations were mostly performed in macrophage specific deletions of either Atg7 or Atg5. The cannabinoid CB2 receptors of macrophages were found to have a protective role in ALD, which was abrogated by Atg5-deletion in macrophages^[301]. Increased mortality in Atg5 deleted mice was also demonstrated after chronic ethanol feeding plus LPS challenge^[329]. Similar findings were reported after Atg7 deletion^[330]. Both studies demonstrated an activation of the inflammasome and an augmented IL-1 production.

In contrast to hepatocytes and macrophages the effect of autophagy in hepatic stellate cells after ethanol exposure has not been clarified. A recent study in immortalized rat stellate cells demonstrated that autophagy could contribute to ethanol-induced stellate cell activation^[331]. Induction of fibrosis by alcohol in current murine models is not feasible unless accompanied by steatosis induced by a high-fat diet^[332].

Most autophagy studies in ALD are focused on the involvement of macroautophagy. Recent evidence however indicates that CMA is also important in alcoholic liver disease through the CMA negative regulator sorting nexin 10 (snx10). Snx10 knockout mice fed with Lieber-DeCarli diet were resistant to alcohol-induced liver injury associated with an increase of lysosome-associated membrane protein 2A (LAMP2A) and CMA activation through inhibition of the enzyme Cathepsin A which

is responsible for LAMP2A degradation^[333]. Deficiency therefore of a CMA negative regulator, protects animals from ALD. Deficiency of another CMA negative regulator, Lipocaline-2 (LCN2), also maintains hepatic CMA activity in murine livers after chronic alcohol administration^[334] verifying the idea that impaired CMA may be responsible at least in part in alcohol-induced liver injury.

Involvement of miRNAs is an additional factor in the regulation of autophagy in ALD that has emerged from recent evidence. Several miRNAs were reported to alter autophagy and alcoholic steatosis^[335]. miR-26a ameliorates alcohol-induced acute liver injury by two MAPKs inhibitors thus inducing Beclin-1 expression and autophagy^[335]. Another report provided evidence that miR-155 is a mediator of alcohol-related exosome production and autophagy impairment in both hepatocytes and macrophages^[336]. Deletion of miR-155 protected mice from alcoholic steatosis and inflammation. Interestingly in this study serum levels of exosomes were increased in ALD patients and alcohol exposed mice, whereas miR-155 deficient mice had significantly reduced exosome release from both hepatocytes and Kupffer cells. It was suggested therefore that autophagy is an atypical promoter of exosome release in ALD.

Clinically important observations indicate that withdrawal of ethanol from ethanol-fed rats resolves steatosis^[337] suggesting that removal of ethanol oxidation and restoration of lipophagy may be the mechanism of steatosis resolution observed in humans after ethanol abstinence^[338,339]. Informative reviews of autophagy in ALD were recently published^[90,181,182,340-342].

In view of the fundamental role of lipophagy in the pathogenesis of ALD, it is not surprising that pharmacological inducers of lipophagy like carvamazepine, rapamycin, resveratrol and simvastatin were tested in alcohol-fed animals with a resultant attenuation of liver lesions. By contrast chloroquine exacerbated hepatic steatosis^[312,343,344]. Recently plant-derived agents were also used to activate lipophagy. Thus, corosolic acid^[345], quercetin^[346] and Salvianolic acid A^[347] all had a favorable result on alcohol-induced liver lesions activating lipophagy through different pathways.

Summarizing, it is evident that whether ethanol causes an increase or decrease of autophagy depends on the duration of ethanol consumption/exposure, the amount of alcohol given, and the manner in which it is administered^[290,302]. Moreover, lipophagy and mitophagy cannot act as defensive mechanisms in the long term as they do in acute ethanol consumption as they are inhibited by chronic alcohol exposure^[102,348].

VIRAL HEPATITIS

In the past decade, hepatic autophagy has been implicated in viral infection with either hepatitis B (HBV) or hepatitis C (HCV).

HBV

Recent studies have shown that autophagy is involved in the life cycle of Hepatitis B. Inhibition of autophagosome formation could reduce HBV production, while stimulation of autophagy could significantly contribute to HBV production^[349,350].

However, the mechanism by which HBV activates autophagy is not clear. Previous reports have implicated either the HBx^[351,352] the large HBsAg protein^[353] or a mutant with a deletion in the preS2 region^[354,355] as inducers of ER stress which in turn increases autophagy.

In contrast it was shown that HBx does not play a significant role in the induction of autophagy compared to the small HBsAg protein also increasing autophagy *via* the induction of ER stress. An HBV genome unable to express small HBsAg does not activate autophagy^[356]. To reconcile the discrepancy, it has been suggested that autophagy can be stimulated both by HBx and the small surface HBsAg protein through upregulation of beclin-1 expression^[357,358]. In addition HBx induces autophagy through its effect on the cytoplasmic high-mobility group box 1 (HMGB1), identified as a positive regulator of autophagy. HBx binds to HMGB1 and triggers autophagy in hepatocytes^[359]. This observation may be clinically relevant. Spontaneous and induced autophagy of peripheral Treg cells from 98 patients with chronic hepatitis B were assessed^[360]. No difference of spontaneous autophagy was found between patients and normal controls but induced autophagy was significantly higher in patients. It was also related to HMGB1 as it was significantly decreased when HMGB1 was blocked with a neutralizing antibody.

HBx further impairs lysosomal acidification with a final result the accumulation of immature lysosomes. Moreover immature lysosomal hydrolase cathepsin D was

shown in human liver tissues with chronic HBV infection suggesting that a repressive effect of HBx on lysosomes may be responsible for the inhibition of autophagic degradation^[350]. Interestingly, although HBV could impair lysosomal acidification it was unable to induce autophagic protein degradation, due to the inability of HBV to increase the sequestration of proteins destined for degradation by autophagy^[350]. Therefore, it is usually stated that HBV induces incomplete autophagy. In addition, it was clearly shown that HBV specifically targets damaged mitochondria and mitophagy. Either the whole HBV genome or HBx alone were able to induce Parkin-mediated mitophagy^[361,362]. In addition, HBx-induced autophagy inhibited mitochondrial apoptosis increasing the survival of HBV DNA-transfected cells^[349]. Another clinically important observation is that different HBV genotypes have a variant effect on autophagy. HBV genotype C was a more potent inducer of autophagy than HBV genotype B. HBV-C is associated with more severe disease than HBV-B but however attractive such an association between autophagy and severity of liver disease may be, it has to be verified^[363,364].

It is important to realize that many viruses, including HBV, have developed strategies to hijack autophagy to benefit their replication and dissemination^[356,365,366]. So far, HBV is the only DNA virus known to exploit autophagy for its own replication as it is RNA, but not DNA viruses, that commonly use autophagic function to promote replication^[367].

HBV infection induced the early-stage formation of autophagic vacuoles increasing the PI(3)K enzyme activity to promote HBV DNA replication. HBx can directly bind and activate the PI3KC3 complex^[368,369]. Ablation of Atg5 has been shown to inhibit autophagy and impair nuclear localization of the HBV core protein. HBV DNA level in sera was decreased by more than 90% accompanied by practically undetectable levels of the HBV DNA replicative intermediate in the liver^[370].

Autophagy was responsible for the degradation of an oncogenic microRNA-224 in the liver of HBV patients with hepatocellular carcinoma (HCC) and HBx-transgenic mice. In HCC patients, the combination of low-Atg5 expression and high miR-224, was significantly correlated with a poor overall survival rate^[371]. The list of the mechanisms used by HBV to subvert autophagy and the detrimental consequences in the liver is by no means complete as new factors are constantly reported including release of pro-inflammatory cytokines and chemokines and inhibition of neutrophil extracellular trap^[372-375].

Further evidence of autophagy subversion by HBV was recently reported. In HBV-replicating hepatocyte cultures, the silencing of Atg5, Atg12, and Atg16L1, interfered with viral core/nucleocapsid (NC) formation/stability and significantly reduced virus yields. It was further demonstrated that a covalent conjugation of Atg12 to Atg5 was essential for HBV replication. In addition the virus required Atg10 and Atg3 which are necessary for Atg5-12 conjugation. Deletion of Atg10 and Atg3 decreased HBV yields, while Atg3 overexpression increased virus production. HBV was associated with the Atg5-12/16L1 *via* interaction of HBV core protein with the Atg12 unit of the complex. Subsequent autophagosome maturation events were not necessary for HBV replication. These data indicate that HBV subverts early, non degradative autophagy components avoiding thus autophagosomal destruction^[178,376,377].

Death receptors of TNFSF10 (tumor necrosis factor superfamily member 10) participate in the immune defense against several viruses by promoting apoptosis. HBx impairs TNFSF10 receptor signaling through autophagy mediated lysosomal and not proteasomal degradation. Importantly a significant reduction of the protein TNFRSF10B was demonstrated not only in cell lines but also in the liver of chronic HBV patients^[378].

It was very recently reported that the hepatitis D virus also utilizes autophagy to assist its life cycle as it increases autophagosome accumulation and impairs autophagic flux. Both the small HDAg and large HDAg proteins are capable to disturb the autophagy machinery, in particular the proteins Atg7, Atg5, and LC3 involved in the early elongation stage of autophagy. Unexpectedly, deletion of Atg5 and Atg7 reduced the intracellular HDV RNA level in hepatocyte cell lines without an effect on HDV secretion^[379]. Reviews of autophagy in HBV have recently been published^[366,380].

HCV

Reported data have shown that HCV could induce autophagy to support its own replication^[381,382]. Several mechanisms for HCV induction of autophagy have been investigated using hepatocyte cell lines^[383,384]. HCV infection initiates the formation of phagophores after induction of the localization of Atg5 to the ER. Phagophores fuse to form autophagosomes. HCV-induced autophagosomes were further reported to be required for viral RNA replication as the autophagosomal membrane provided a

platform containing HCV NS5A, NS5B, and viral RNA for replication^[385-387] but subsequently HCV blocks the fusion of autophagosomes and lysosomes through Rubicon overexpression. As a result autophagosomes accumulate and HCV RNA replication and assembly of infectious virions^[385,388,389,390,391] are supported.

However, several studies have contradicted the need for co-localization of viral proteins in the autophagosomal membrane suggesting that this is not a necessity for viral replication^[392-395].

Autophagy favors HCV replication with an additional mechanism. The entire autophagic process may be manipulated leading to the suppression of the HCV associated innate antiviral response^[393,396]. After silencing different Atgs, HCV viral infectivity was suppressed in parallel with an upregulation of interferon-stimulated gene expression^[390]. Moreover, HCV seems to activate autophagy to degrade the tumor necrosis factor receptor-associated factor 6 (TRAF6), thus subverting innate host immunity^[389,397-399]. HCV induced unfolded protein response strongly activates autophagy to sustain viral replication through inhibition of cellular apoptosis^[396]. Different HCV genotypes may have variable influence on autophagy^[391,400].

HCV was also found to selectively activate lipophagy to counteract the HCV induced lipid abnormalities. This may be clinically important as the levels of autophagy in the liver of chronic HCV patients were inversely correlated to steatosis^[401]. Inhibition of autophagic degradation of lipophagy may account for the characteristic occurrence of hepatic steatosis in chronic HCV infection. Mitophagy is also selectively activated *via* the PINK1-Parkin axis in infected cells, thereby promoting HCV viral RNA replication^[361,402]. Virus-activated mitophagy further attenuates apoptosis and favors persistent viral infection^[403]. In agreement with this finding, the viral non-structural protein 5A (NS5A) was shown to disrupt mitochondrial dynamics, thus increasing ROS production and mitophagy^[404].

On the other hand, the viral core protein interacts with Parkin inhibiting its translocation to mitochondria. Mitophagy is suppressed and mitochondrial injury of infected hepatocytes is sustained and viral persistence is maintained^[405].

Syntaxin 17 is an autophagosomal protein required for the fusion of autophagosomes with lysosomes and also the release of HCV. The amount of syntaxin 17 was reduced in HCV-replicating cells indicating that HCV impairs the late stages of autophagy affecting the equilibrium between the release and the lysosomal degradation of viral particles^[406].

Recently CMA was also demonstrated to be activated by HCV leading to degradation of IFN- α receptor-1^[407]. Moreover the HCV NS5A was found to interact with Hsc70, recruiting Hsc70 to hepatocyte nuclear factor 1 α thus targeting HNF-1 α for CMA degradation^[408]. Taken together these studies indicate that HCV induced CMA also facilitate HCV replication.

However, an opposite less permissive effect of the manipulation of autophagy by HCV has been suggested as a result of recent studies. Atg10 is critical for autophagy as it promotes the Atg5-Atg12 complex formation. Two isoforms of the Atg10 protein were described, namely Atg10 (a longer one) and Atg10S. They have a similar amino acid sequence except for an absence of a 36-amino acid fragment in Atg10S. Yet they differ in their effects on HCV genome replication. Atg10 with deleted or mutated two cysteins, (Cys⁴⁴ and Cys¹³⁵) could trigger the expression of anti-HCV immunological genes combating the HCV replication^[409,410].

Taken together these results indicate that autophagy is required for initiation of the HCV replicative phase but not for further replication^[393]. However this might not be entirely true, as chloroquine an inhibitor of lysosomal acidification inhibits HCV replication offering an additional evidence for the permissive role of autophagy in HCV infectivity in the late phase^[411].

Autophagy may additionally be involved in HCV replication through the regulation of the exosomal pathway^[390] and apolipoprotein transport^[412], both critical steps in the egress of the HCV virion. The virion is associated to apolipoprotein E (ApoE) and its infectivity is enhanced. Autophagy has a central role in the trafficking of ApoE in HCV-infected cells leading to partial autophagic degradation of ApoE, but also to the interaction between ApoE and the viral protein E2 to increase the production of infectious viral particles^[412]. Molecular details of how HCV is using autophagy to its own advantage were recently published^[380,413].

In summary, the life cycles of HBV and HCV in liver cells can be subdivided into 7 steps: Endocytosis, uncoating, genome replication, translation, envelopment, assembly and release. Both HBV and HCV drive autophagy largely by the ER stress response resulting from uncontrolled translation of viral proteins^[414-416]. In addition HBx modulates autophagy for the benefit of HBV replication^[357], while multiple HCV proteins including p7, NS3/4A and NS4B, modulate autophagy by direct or indirect

association with moieties of the early autophagy machinery in favor of its replication^[417-419]. Pharmacological or genetic manipulation of autophagy may limit the viral yield^[183,369,420], making autophagy a feasible target for HBV and HCV treatment.

FIBROSIS-CIRRHOSIS

The liver responds to practically any insult with only a limited number of pathological lesions: Hepatitis (hepatocyte death), cholestasis, fibrosis-cirrhosis or a combination of the three. Autophagy participates in all liver pathological responses.

Liver fibrosis is a complex and dynamic cellular process implicated in the evolution of the majority of chronic liver disease towards cirrhosis. Most review articles have broadly concentrated on the role of autophagy in liver diseases, with restricted information on cell types implicated in liver fibrosis. Not unexpectedly, most research has focused on hepatic stellate cells (HSCs) and myofibroblasts, because they are the central elements in extracellular matrix production^[421]. However, other liver cells, including hepatocytes, macrophages, sinusoidal endothelial cells (LSECs), infiltrating immune cells and the so-called ductular reaction (DR) are also important^[422,423]. DR significantly correlates with the degree of fibrosis and involves cholangiocyte-like cells that dominate an interplay of extracellular matrix and inflammatory infiltrate^[424-427].

HSC and autophagy

The fundamental event in fibrosis is the transformation of hepatic stellate cells into myofibroblasts and this is closely related to autophagy. Typical autophagosomes that contained LDs were found in cultured HSCs indicating a connection of liver fibrosis and lipid autophagy^[428]. Increasing evidence supports the notion that inhibition of lipophagy in hepatocytes reduces HSC activation and fibrosis progression^[429,430]. Inhibition of the activation of HSCs and the formation of autophagosomes have been reported and these seem to be connected with the downregulation of transforming growth factor beta 1/Smads pathway as an increase in TGFb/Smad3 Leads the transcription of Beclin-1, which is a critical player in the autophagy process^[431-433].

In rat-derived HSCs, cytoplasmic LDs are degraded followed by fibrogenic genes expression. Moreover induced lipid accumulation by an alkaloid, was associated with quiescent HSCs due to autophagy blockade^[434]. Inhibition of autophagy by chloroquine improved CCl4-induced liver fibrosis affecting the activation of hepatic stellate cells as expected^[435]. On the other hand, dihydroceramide an inhibitor of autophagy promoted the progression of liver steatosis to fibrosis^[436]. Similarly, inhibition of YAP degradation also led to liver fibrosis^[113].

In addition, it has been suggested that the IL-17A/STAT3 signaling pathway is important in the evolution of liver fibrosis through suppression of hepatocellular autophagy since neutralization of IL-17A promotes the resolution of experimental fibrosis^[437].

Based therefore on current evidence, it has been stated that autophagy at least in murine hepatocytes is a selective survival mechanism through clearance of excessive fat leading to attenuation of lipotoxicity^[438]. This is certainly not the case for HSCs autophagy where lipid droplets are digested to supply energy for the activation of HSCs, promoting thus liver fibrosis. Non specific inhibition of stellate cell autophagy or specific inhibition of Atg5 or Atg7, blocked HSCs activation^[439-441]. Lipophagy in HSCs is induced by ER stress^[442] and is mediated through Rab25 in a ROS dependent manner as antioxidants were effective in stopping autophagy^[87]. In agreement with experimental data, clinical research found that cirrhotic patients had significantly increased levels of several autophagy- related genes compared with non cirrhotics accompanied by increased maturation of lysosomal cathepsin D^[85]. Furthermore, serum lipids were evaluated in patients with cirrhosis of viral etiology and compared to non cirrhotics. Low serum lipids were found in HCV and HBV cirrhosis which were negatively correlated with lipophagy^[443].

Micro-RNAs interfere with the activation of stellate cells. miR-16 inhibits the expression of guanine nucleotide-binding -subunit 12 (G12) which is overexpressed during fibrogenesis and facilitates Atg12-5 formation, thus activating stellate cells^[444]. Also miR-181-5p transferred to mouse HSCs *via* exosomes from engineered adipose derived stem cells led to inhibition of fibrosis^[445].

Several signals can induce autophagy in HSCs^[180], including hypoxia-inducible factor-1alpha^[446], transforming growth factor 1^[447], as well as the danger-associated pattern molecule high-mobility group box-1 (HMGB-1)^[448]. Additional signals like ROS-JNK1/2 and the XBP1 arm of the Unfolded Protein Response have also been

identified as necessary requirements of HSCs activation through autophagy^[449,450]. TGF- β 1 has also been reported to mediate autophagy^[440]. Similarly, HSCs in cell culture with depleted Atg2A fail to spontaneously trans-differentiate^[451]. Quercetin attenuated hepatic fibrosis in mice through inhibition of hepatic HSC activation and autophagy^[452].

Selective activation of mitophagy in HSCs also favors fibrosis. PM2.5 is an air pollutant that activates HSCs and initiates liver fibrosis. This is due to increased ROS production and induction of mitophagy through activation of the Pink1/Parkin pathway^[453]. In contrast, inhibition of mitophagy was shown to promote inflammation^[454] due to dissemination of inflammatory signals from HSCs production of inflammatory cytokines^[455]. However very recently it was reported that selective inhibition of mitophagy in macrophages attenuates fibrosis. Mice Kupffer cells from CCL4-induced acute injury showed increased ROS production, activated mitophagy and increased TGF- β 1 secretion. T-cell immunoglobulin domain and mucin domain-4 (TIM-4) interference in Kupffer cells inhibited Akt1-mediated ROS production and decreased mitophagy and TGF- β 1 secretion through suppression of PINK1/Parkin, to ameliorate CCL4-induced hepatic fibrosis^[456]. Seemingly in disagreement with this notion, is the finding that the autophagic protein p62/SQSTM1, a negative controller of HSC activation is downregulated in trans-differentiating HSCs associated with hepatocellular carcinoma. P62 ablation increases fibrogenesis but this is not related to autophagy but rather to the reduction of p62-dependent activation of the vitamin D receptor (VDR) and the resultant loss of repression of HSC by VDR agonists^[457,458].

Even in HSCs the characterization of autophagy as a double-edged sword has been justified. A novel molecular mechanism of selective autophagy in HSCs indicates that autophagy may also protect from liver fibrosis. The RNA-binding protein ELAVL1/HuR plays a crucial role in regulating ferroptosis in liver fibrosis. ELAV1 enhances ferritinophagy leading to ferroptosis of HSCs and attenuation of liver fibrosis^[459]. Despite this report, most existing evidence indicate that activation of HSCs autophagy is pro-fibrogenic, therefore a selective block of autophagy in fibrogenic cells might be an attractive future anti-fibrotic therapy^[90].

The opposite seems to happen in hepatic macrophages^[55] where activation of autophagy is anti-fibrogenic^[460]. Mice macrophages with specific deletion of atg5, secreted increased levels of ROS-induced IL-1A and IL-1B. In addition, liver myofibroblasts incubated with the conditioned medium of Atg5(-/-) macrophages expressed increased pro-fibrogenic genes. Attenuation of fibrosis was achieved after IL-1 neutralization indicating that IL1A/B are critical mediators of the profibrotic effects of autophagy inhibition in macrophages^[461-463]. Autophagy in Kupffer cells is counteracted by the enzyme monoacylglycerol lipase catalyzing the production of arachidonic acid leading to inflammatory macrophage activation and fibrosis^[464].

On the other hand deletion of Atg7 in sinusoidal endothelial cells (LSECs) demonstrated that the selective loss of their autophagy led to cellular dysfunction and decreased intrahepatic nitric oxide. Impairment of autophagy after CCL4-induced acute liver injury in rats, also impaired handling of oxidative stress by LSECs and amplified liver fibrosis^[465].

Similarly, autophagy defective sinusoidal endothelial cells (LSECs) as demonstrated in patients with NASH favor advancement of fibrosis^[282]. At the same time, even excessive autophagy activation may lead to caveolin-1 degradation, thus worsening the LSECs defenestration and ultimately promoting fibrosis^[466]. Therefore, any dysregulation of autophagy in LSECs may aggravate liver fibrosis^[467].

An elegant immunofluorescence study of cirrhotic livers linked autophagy with an additional population of fibrogenic cells other than HSCs, the reactive ductular cells (RDC) which were characterized as cholangiocyte-like epithelial cells positive for cytokeratin 19^[85]. They are responsible for ductular reaction (DR), a common response to various insults of the liver implicated in the pathogenesis of cirrhosis^[432]. Administration of chloroquine, reduced the expression of CK19 positive RDC and blunted liver fibrosis^[86]. DR parallels HSC activation in many liver diseases^[430]. Reactive ductular cells secrete soluble pro-fibrogenic factors targeting HSCs and myofibroblasts^[468]. Recently it was demonstrated that in cirrhotic human livers, RDCs with activated autophagy also had upregulated expression of TGF and fibroblast specific protein-1^[469] making autophagy a necessary requirement during the DR process. The role of autophagy in liver fibrosis is therefore complex and the end result depends on the cell population involved. In general, HSCs and RDCs have a pro-fibrogenic effect. On the contrary, autophagy counteracts fibrogenesis acting in hepatocytes, macrophages and LSECs^[470].

HCC

The role of autophagy in tumor cell biology has not been fully elucidated. Autophagy has both pro- and anti-tumorigenic roles. For example, it can either inhibit inflammation acting as an anti-oncogen or protect tumor cells from ROS damage acting as a pro-oncogen^[471,472].

Opposing effects have been reported. Activated Ras requires autophagy to maintain oxidative metabolism and tumorigenesis^[473]. On the other hand, Ras-induced expression of two proteins Noxa and Beclin-1 promotes autophagic cell death, limiting thus the oncogenic potential of deregulated Ras signals^[474]. Drugs like ursodexocholic acid can efficiently eliminate resistant to other drugs cancer cells through induction of autophagic death^[475].

HCC is one of the most common types of liver cancer^[476]. Most of the HCC cases are accompanied by cirrhosis that results from long-standing chronic inflammation due to viral hepatitis or non-viral etiologies including heavy alcohol intake, NAFLD, autoimmune hepatitis, primary biliary cholangitis, and hemochromatosis^[477].

Mice with impaired autophagy are unable to develop HCC even after of strong challenge. This was related to the induction of tumor suppressors like p53^[478]. However, after initiation of HCC, the presence of autophagy is required to degrade tumor suppressors promoting thus the development of HCC^[86]. Both macroautophagy and CMA are implicated as a double edge sword in liver tumorigenesis^[479].

Autophagy has a dual role in hepatocellular carcinoma (HCC). It is an anti-cancer mechanism in the dysplastic stage of HCC initiation, while it favors HCC development and confers resistance to treatment^[480,481]. This is possibly due to the maintenance of mitochondrial integrity and protection of cells against oxidative stress during HCC initiation, followed by the downregulation of tumor suppressors to promote the development of HCC^[86,482].

In a study of 156 HCC patients increased levels of the autophagy marker LC3B are associated with a dismal prognosis^[483]. Higher levels of LC3-II were associated with lymph nodes metastasis, higher vascular invasion and reduced 5-year survival^[484].

Macroautophagy may also have an anti-oncogenic function, as reduction of either Atg5 or Atg7 Levels lead to appearance of multiple liver tumors^[485]. Similarly, low levels of autophagic proteins and activity are associated with bad prognosis of human HCC^[486,487]. Beclin-1 Levels are lower in HCC tissue samples compared to normal tissue from the same patient. Beclin-1 expression was studied in 300 HCC patients. A correlation with disease-free survival and overall survival was found only in the Bcl-xL+ve patients. It was suggested therefore that a synergy of defective autophagy and altered apoptotic activity lead to tumor progression and reduced survival^[488].

Inhibition of autophagy leads to the accumulation of SQSTM1/p62. Accumulation of p62 on the one hand may protect from HCC initiation as it blocks the antioxidant functions of nuclear factor erythroid-2-related factor 2 (Nrf2)^[489-492]. On the other hand, accumulation of p62 also contributes to carcinogenesis through persistent activation of Nrf2^[493]. Nrf2 expression promotes the development of HCC^[493]. Deletion of p62 in autophagy defective livers counteracts tumorigenesis. Therefore an accumulation of p62 is partly responsible for the increase in hepatic tumors, *via* the activation of Nrf2^[492-494]. The activation of Nrf2 turns glucose and glutamine into anabolic pathways supporting tumor cell proliferation^[176,495]. In addition, autophagy inhibits malignant transformation in the liver through Yes associated protein 1 (YAP1) degradation, a protein with a crucial role in hepatic oncogenesis^[113,496].

Aberrant activation of the Wnt/ β -catenin signaling is another critical pathway in the onset and development of HCC. A recent study reported that the Wnt/ β -catenin inhibitors exert anti-tumor effects on HCC cells by regulating autophagy^[497]. However this is in disagreement with a previous report where interfering with Wnt secretion in HCC cell lines does not affect autophagy or the level of β -catenin signaling despite cell growth suppression indicating that other mechanisms might underlie the growth-suppressive effect^[498].

Furthermore, the activation of autophagy was shown to mediate inhibition of proliferation and induction of apoptosis of hepatoma cell through several mechanisms^[499-506]. The induction of autophagy by concanavalin A or different chemotherapeutic drugs in murine livers inhibit hepatoma cell growth and prolongs survival^[507-519]. On the other hand suppression of autophagy was reported to enhance the susceptibility of hepatocellular cancer cells towards a variety of chemotherapeutic agents^[108,520-529].

Several microRNAs (miRNAs) have been implicated in HCC tumorigenesis. miR-204 reduces tumor autophagy in HCC^[530]. Moreover autophagy degradation of miRNA-224 suppressed the growth of HBV-related HCC^[371], while miR-375 which is

downregulated in HCC was reported to inhibit autophagy by decreasing the expression of Atg7 and autophagic flux. Up-regulation of miR-375 inhibits mitophagy of HCC cells, reduces the elimination of damaged mitochondria, and decreases cell viability^[99]. miR-26 could inhibit autophagy and enhance chemosensitivity of HCC cells^[531].

LncRNAs are another set of ncRNAs with a length exceeding 200 nucleotides without translation into proteins^[109]. Several lncRNAs, like Hnf1a-as1, Hotair and Hulc promote autophagy and function as oncogenes in HCC^[106-109].

The role of mitophagy and lipophagy is also important in HCC growth acting as a double edge sword. Increased mitophagy by concanavalin A, adriamycin or curcumin was shown to suppress hepatoma cell growth^[507,510,517,530] while melatonin increased the sensitivity of human hepatoma cells to sorafenib by triggering mitophagy^[532]. A recent study also demonstrated that inhibition of inflammasome activation and induction of mitophagy suppressed HCC growth^[533]. On the other hand it has been demonstrated that increased mitophagy may facilitate HCC cell survival either through ROS production or attenuation of p53 activity^[534,535].

Lipophagy can also act both ways. On the one hand, it can allow tumor cells to have access to a supply of energy critical to their growth^[536] and on the other hand, lysosomal acid lipase, the lipase that facilitates lipophagy, exhibits tumor suppressor activity^[537]. Lipophagy was also reported to induce apoptosis *in vitro*, via induction of ER and mitochondrial stress^[538]. CCAAT enhancer binding protein a, a protein that is upregulated in HCC patients, increases resistance to energy starvation and favors carcinogenesis through lipophagy^[539].

In addition to the general characteristics of autophagy implication in HCC, there are certain points to be mentioned in specific liver disease associated HCC. As mentioned before, autophagy is activated by the HBx protein^[357,369] and this may be related to HBV carcinogenesis. Increased autophagosome formation by HBx was accompanied by decreased degradation of LC3 and SQSTM1/p62 and greatly impaired lysosomal acidification and accumulation of immature Cathepsin D. These data may indicate that repression of lysosomal function by HBx could be important for the initiation and progress of HBV-associated HCC^[350].

CMA and cancer metabolism are also interconnected. Once malignant transformation occurs, CMA activity is significantly increased in cancer cells so that the new metabolic requirements are maintained^[64]. Blockade of CMA which is upregulated in several cancers reduces progression and metastatic potential of solid tumors because the characteristic increased rates of aerobic glycolysis are reduced in a p53-dependent manner^[540]. Macroautophagy and CMA seems to be interconnected and often substitute for one another as in the case of HCC. Under physiological conditions there is no expression of p62 in normal livers pointing to macroautophagy as the main mechanism facilitating cell survival. However in a recent study of 46 cirrhotic livers it was shown that p62 was increased indicating an impairment of macroautophagy, but LAMP-2A and heat shock protein 70 were uniformly increased indicating that an upregulated CMA was trying to compensate for the reduced macroautophagy and therefore promote HCC survival. Moreover, hydroxychloroquine inhibition of lysosomal degradation led to induction of the tumor suppressor p53 and promotion of apoptosis^[541]. HCV is also an inducer of HCC. During HCV infection, increased cellular stress has been reported. Severe stress promotes Nrf2 transcription which in turn is responsible for CMA activation resulting in the suppression of hepatic innate immunity and possible degradation of tumor suppressors. The subsequent oncogenic cell programming initiated by a cytoplasmic virus like HCV, has been recently described in detail^[542].

Defective autophagy is linked to MAFLD-related HCC, because the accumulated p62/SQSTM1, induces the oncogenic NF-κB activity while retained damaged mitochondria and produced ROS to damage cellular DNA^[543]. A novel mechanism was recently reported in ethanol induced liver disease and HCC. Tumor necrosis factor-α-induced protein 8 (TNFAIP8) has been associated with tumor progression in several cancer types including the initiation of HCC. TNFAIP8 induced autophagy in liver cancer cells through blocking of AKT/mTOR signaling and direct interaction with ATg3-Atg7 proteins. This mechanism is operative in alcohol related liver disease in mice and humans but not in high-fat-fed obese mice or patients with MAFLD^[544]. Details of the molecular mechanisms of autophagy in both protection and promotion of HCC were recently published^[545-547].

An additional aspect of HCC biology where autophagy plays an important role is the involvement of tumor-associated macrophages and tumor microenvironment. They are polarized after implication of sensing factors from tumor environment and autophagy^[130,548]. Deficiency of TLR2 decreased the liver production of TNFα, IFN

gamma and IL1a/b accompanied by reduction of autophagy flux and increase in oxidative stress and p62 aggregates in liver tissue. These changes were associated with increased carcinogenesis and progression of HCC^[549]. Enhancement of autophagy in tumor-associated macrophages leads to M1 polarization which reduces tumor progression while M2 polarization is permissive for tumorigenesis^[550]. The mTOR-TSC2 pathway, a key negative regulator of autophagy, is crucial for macrophage polarization since its activation leads to M2 phenotype. It was recently shown that the coagulants tissue factor (TF) and factor VII (FVII) produced in tumor microenvironment, are implicated in HCC growth promotion by suppression of autophagy mediated through mTOR activation and Atg7^[551].

In view of the variable functions of autophagy, there should be an individualized approach of autophagy manipulations for HCC treatment. Thus, various lysosomal inhibitors including chloroquine and hydroxychloroquine have been used as treatment either as sole agents or in combinations with other treatment modalities in a variety of murine HCC models^[523,552,553]. Interference with autophagy may be a sound therapeutic option for the treatment of HCC^[554,555]. Based on the fact that autophagy is upregulated in metastatic HCC^[556] use of autophagy inhibitors like chloroquine and hydroxychloroquine in combination with other drugs may be a better option for treating metastatic HCC in humans. A combination of a number of drugs with autophagy inducers have been used to target cancer cells. A combination of percutaneous transarterial chemoembolization with chloroquine, was associated with increased tumor cell necrosis and apoptosis^[557] and might counteract the presence of residual hepatocellular carcinoma cells^[558,559]. Sorafenib, a multikinase inhibitor approved for HCC treatment, induces autophagy^[560] and data show that a combination with autophagy inhibitors increase tumor response^[537,561].

Cholangiocarcinoma

Xenografts in nude mice are widely used models of cholangiocarcinoma (CCA). Activated autophagy has been reported in tumor cells from such a model and in specimens from CCA patients^[562]. LC3B, Beclin 1, and p62/SQSTM1 expressions were additionally found to be increased at the initial stage of the multistep cholangiocarcinogenesis^[563]. However, a lower Beclin 1 expression was associated with metastatic lymph node disease and poor survival of patients with intrahepatic CCA^[564,565]. Apoptosis was induced in cholangiocellular cell lines and tumor development was suppressed in a mice xenograft model after interference with autophagy^[562]. Similarly, suppression of autophagy by chloroquine increased the chemosensitivity of cisplatin-treated CCA cells^[566] and increased apoptosis of CCA cells through ER stress^[567]. Chloroquine blockade of autophagy inhibited the tumor growth in Kras/p53 intrahepatic CCA^[568,569]. CCA is extremely resistant to chemotherapy. 5-fluorouracil (5-FU) induced autophagy in CCA cells^[570] while autophagy inhibition by capsaicin was followed by repression of malignant cell growth^[570], indicating that autophagy may be implicated in the multidrug resistance of this tumor. Autophagy was also induced after incubation of CCA cells with the sphingosine kinase 2 inhibitor, ABC294640. Inhibition of autophagy by chloroquine potentiated ABC294640-induced apoptosis^[571]. Modulation of autophagy therefore may be helpful in CCA treatment.

INHERITED METABOLIC DISEASES

A1 antitrypsin deficiency and fibrinogen storage disease

Autophagy is also implicated in other types of liver injury like the inherited metabolic diseases. Alpha 1-antitrypsin deficiency is the most extensively studied. Alpha 1-AT is a glycoprotein inhibitor of destructive neutrophil proteases^[572,573]. Several naturally occurring mutants of alpha1-AT, have been shown to participate in the pathogenesis of human diseases, such as chronic liver-associated diseases^[574-576]. The Z mutation resulting from a single G->A transition in codon 342, generates a mutant protein that forms aggregates in the hepatocytes^[577]. Liver injury is caused by the retention of this polymerized mutant alpha1-ATZ molecule in the ER of hepatocytes followed by an induction of autophagic response. Removal of the insoluble alpha-1 anti-trypsin by the autophagosome is the mechanism by which the activation of autophagy protects the liver in alpha1-antitrypsin deficiency^[578-581]. In earlier studies, liver injury was associated with mitophagy indicating that the ER retention of alpha(1)-ATZ led to involvement of the mitochondria, with specific patterns of mitochondrial dysfunction and mitochondrial injury^[582,583].

Genetic studies in mice have shown that deletion of Atg5 led to an increased retention of alpha 1-ATZ^[584] and that deficiency of Atg6 and Atg14 in yeasts inhibited alpha1-ATZ degradation^[585]. Similarly, the induction of autophagy in mice by rapamycin reduced liver alpha1-ATZ aggregation and liver injury^[582,586-589]. These findings have been repeated and verified when enhancement of autophagy^[590] with either carbamazepine^[591], gene transfer of the autophagy regulator TFEB^[592] or an analog of glibenclamide^[593] reduced the toxic protein. Recent preclinical studies have also demonstrated that an exogenous bile acid like norursodeoxycholic acid may be clinically useful in this condition^[594,595].

Fibrinogen storage disease is a very rare autosomal-dominant ER storage disease presented with hypofibrinogenemia, elevated transaminases, accumulation of fibrinogen aggregates in the ER of hepatocytes and several fold increase of autophagocytic vacuoles. Some patients progress to cirrhosis similar to alpha-1-AT deficiency. A clinical study of eight patients has showed that administration of carbamazepine at low anticonvulsive dosage led to rapid normalization of alanine-aminotransferase indicating a critical role of autophagy in this disease^[596].

Wilson's disease

Wilson disease is an inherited disease of copper metabolism linked to hundreds of mutations in the ATP7B gene^[597]. Recent evidence based on studies from hepatocytes of patients and ATP7b deleted mice has shown the presence of an increased number of autophagosomes, indicating the activation of an autophagic response to prevent copper associated cell death^[598]. Moreover, inhibition of autophagy accelerated hepatocyte death whereas increased autophagy by either starvation or TFEB overexpression had a cytoprotective effects^[598]. Autophagy therefore seems to be a major protective mechanism for hepatocytes in copper accumulation. These findings may lead to the use of autophagy inducers like carbamazepine as a future potential treatment of Wilson's disease.

Glycogen storage disease

Glycogen storage disease type 1a (GSD1a) is an inherited hepatic disease associated with decreased autophagic flux as a consequence of defects in the glucose-6-phosphatase a, that converts glucose-6-phosphate into glucose. These abnormalities lead to glycogen and lipid accumulation in hepatocytes^[599]. GSD1a is associated with the down regulation of several components of the autophagy machinery^[600].

GSD1a has also been associated with defective sirtuin 1 (SIRT1) signaling leading to impairment of TFEB activity. As in other storage diseases, pharmacological or genetic activation of autophagy reduces the accumulation of glycogen and lipids in cellular and animal models^[601].

VARIOUS DISEASES

Autophagy in the liver is implicated in other diseases as well. An important point that should always be remembered is that the liver is the site of almost 80% of body macrophages and therefore innate immunity can be deeply involved in liver and other organ abnormalities through impaired autophagy of Kupffer cells. Sepsis is the main paradigm of this notion.

Sepsis and liver autophagy

Infection can lead to a systemic multi-organ inflammatory response. Macrophages, play a critical role as they are the most important cells of the innate immunity. Autophagy induction is protective in sepsis through regulation of macrophage polarization. Negative regulation of macrophage activation inhibits inflammasome activation^[602]. Autophagy also interferes with macrophage apoptosis. Uncontrolled autophagy however may lead to autophagy death of macrophages with additional aggravation of inflammation and the so called cytokine storm^[603]. A current example is possibly the SARS-Cov-2 pandemic^[604]. Interestingly, autophagy-deficient macrophages after LPS stimulation over-secrete macrophage migration inhibitory factor and aggravate inflammation^[605]. Other mechanisms are also involved including signaling pathways such as NF-κB, mTOR, and PI3K/AKT^[603].

Mitophagy and mitochondrial dysfunction seem to be also a fundamental factor in multiple organ failure caused by sepsis^[606]. It has been shown that mtDNA liberated from damaged mitochondria, induces a cascade of inflammatory responses^[607-609]. Mitophagy therefore is of great importance for the protection against oxidative stress

during sepsis. It should be noted however that mitophagy defects in the liver, are not the only cause of organ or cell damage during sepsis^[610]. Nonetheless, the liver is the main organ responsible for sepsis-induced damage^[611]. Autophagy is an important protective mechanism in septic liver injury. Increased autophagy can play a protective role in liver function in septic conditions where the activation of autophagy is mediated through activating transcription factor 4 (ATF4). ATF4 is inhibited 48 h after LPS-induced acute liver injury and reversed after obeticholic acid treatment^[612]. Autophagy inhibitors or AMPK inhibitors administration reduced the protective mitochondrial function in LPS-induced human hepatocyte injury^[613,614]. Mitophagy is also involved in apoptosis of CD4+ve T cells which is the main mechanism of immune inhibition during sepsis. Mitofusin 2 (Mfn2) is a mitochondrial outer membrane protein and a negative regulator of autophagy which is increased in sepsis leading to inhibition of autophagy and increase in apoptosis of CD4ve+ T cells^[615]. Autophagy defects can affect antigen presentation by T cells leading to immunosuppression as in the case of Atg5 deficiency^[616]. The role of autophagy in sepsis has been recently reviewed^[617].

Acetaminophen liver damage

Autophagy is also implicated in acetaminophen induced liver disease. There is evidence that increased autophagy is protective against acetaminophen (APAP)-induced liver damage^[618,619]. Pathogenetically, APAP was reported to form APAP-protein adducts in hepatocytes of mice and humans^[620]. Adducts localized in mitochondria contribute to APAP-induced mitochondrial dysfunction and subsequent oxidant stress^[621,622]. Therefore, it is plausible that removal of APAP-adducts will help to ameliorate APAP-induced mitochondrial damage and maintain hepatocyte integrity^[41,623,624]. Experimental evidence indicates that autophagy is mostly responsible for the removal of APAP-adducts^[625]. Moreover administration of adiponectin was found to attenuate APAP-induced injury activating AMPK mediated autophagy^[626]. Activation of autophagy by rapamycin also attenuates APAP-induced liver injury, whereas inhibition of autophagy by chloroquine or deletion of Atg7 in hepatocytes deteriorates liver damage^[153,627]. There is also evidence that autophagy is activated after APAP overdose in specific liver zones^[53].

Somewhat different results were recently presented. Unc-51-like autophagy activating kinase 1 and 2 (Ulk1/2) are important autophagy initiation regulators. Unexpectedly, Ulk1/2 double knockout mice have normal autophagic activity after fasting, but are exceptionally resistant to APAP-induced liver injury possibly indicating that autophagy-dependent and independent ULK1/2 pathways have opposing effects in APAP-induced liver injury^[628].

Reduction of ROS and repression of apoptosis by autophagy is also essential for hepatic regeneration after APAP-induced acute liver failure^[520,627]. A very recent report confirmed that increased autophagy by rapamycin protects mice against APAP hepatotoxicity while chloroquine enhanced liver injury. Importantly it was demonstrated that APAP overdose activated PINK1/Parkin-mediated mitophagy and increased the expression of NF- κ B and NLRP3 inflammasome signaling. These findings were reversed by rapamycin and augmented by chloroquine indicating the critical role of mitophagy in APAP hepatotoxicity^[629].

Interestingly it was reported that infusion of human amniotic mesenchymal stromal cells ameliorated the APAP liver injury through promotion of Kupffer cell M2 polarization and reduction of Kupffer cell autophagy. These results suggest that Kupffer cell autophagy has an opposite effect on APAP hepatotoxicity compared to hepatocytes. This last observation may be useful for future therapeutic exploitation^[630].

Acute liver failure

Acute liver failure (ALF) is a serious syndrome of different etiologies with high mortality^[631]. HSCs implication is significant in ALF. Temporarily increased fibrosis in ALF is probably beneficial serving as scaffolding that maintains regenerating hepatocytes and hepatic integrity^[437,632,633]. Data from a murine APAP induced ALF model have demonstrated that mortality was significantly increased in HSCs depleted animals^[633]. HSCs cannot usually regenerate during ALF due to the submassive necrosis. Autophagy seems to be implicated^[634]. The significance of HSCs survival has been verified in a study of patients with HBV induced acute liver failure. ALF was accompanied by fibrosis and HSCs activation and autophagy induction. It was shown for the first time that the High Mobility Group Box 1 (HMGB1) protein is a powerful inducer of autophagy responsible for HSCs survival^[635].

As mentioned before, autophagy is crucial for HSCs activation which in turn maintains the liver architecture thus preventing the liver scaffold collapse during ALF.

Nitric oxide induces HSCs apoptosis through generation of ROS^[636]. There is evidence however that nitric oxide is also involved in the regulation of autophagy in ALF. Observations in human liver tissue showed an inhibition of autophagy in HSCs while further *in vitro* experiments demonstrated that nitric oxide inhibited autophagy and increased apoptosis of HSCs. These findings were reproduced by chloroquine and reversed by the autophagy inducer rapamycin. Therefore, nitric oxide impairment of HSCs survival may be a decisive factor for the devastating effects of ALF^[637].

An additional clinical and experimental study verified the significance of intact mitophagy in ALF. One of the measurements of oxidative stress is the level of superoxide dismutase (SOD). The serum superoxide dismutase was significantly increased in ALF patients, correlating with the MELD-Na score. SOD levels returned to normal in the remission stage of ALF. In liver tissue from ALF patients and mice models, manganese-dependent SOD was overexpressed and mitophagy in HSCs was inhibited by ROS. Inhibition of mitophagy promoted inflammation in HSCs which was reversed by a mitophagy inducer^[454].

Acute liver damage

Autophagy also protects hepatocytes from acute liver injury, a characteristic of viral hepatitis and acute alcoholic and non-alcoholic steatohepatitis. Mechanisms and cells involved are different as both direct and indirect effects on hepatocytes and macrophages are implicated. Direct effects include autophagy dependent inhibition of caspase 8 in hepatocytes^[638], while indirect effects on macrophages involve limitation of NF- κ B-mediated inflammation and inflammasome-dependent IL-1 β production through p62-dependent mitophagy^[462,639]. Reduced macrophage autophagy can induce pro-inflammatory macrophage polarization and increase the immune mediated acute damage in obese mice^[131]. The TAM family of RTKs (receptor tyrosine kinases), which is expressed in macrophages, has been reported to alleviate inflammation. AXL is the only member of the TAM family that induces autophagy in macrophages and ameliorates hepatic inflammatory responses inhibiting the NLRP3 inflammasome activation in murine macrophages^[640].

The role of Kupffer cells (KCs) is significant in the pathogenesis of acute liver injury. In a murine model of thioacetamide induced acute liver injury it was shown that hyperglycemia aggravated the liver lesions activating the NLRP3 inflammasome of Kupffer cells *via* inhibition of AMPK/mTOR-mediated autophagy. Interestingly, AMPK activation or mTOR signaling deletion restored autophagy and subsequently inhibited inflammasome activation in Kupffer cells^[641]. Spermine is an anti-oxidative polyamine with autophagy induction properties. In a model of acute liver injury, spermine pre-treatment ameliorated liver injury and intrahepatic inflammation by promoting M2 polarization of Kupffer cells.

Furthermore, spermine increased autophagy in KCs. Deletion of Atg5 in spermine treated KCs greatly increased pro-inflammatory cytokines and reduced the anti-inflammatory cytokine IL-10^[642].

LSECs are also involved in acute liver injury. Selective impairment of autophagy in liver endothelial cells increases oxidative stress, thus leading to fibrosis in acute injury^[465].

Ischemia/reperfusion injury

The central role of autophagy in ischemia/reperfusion injury (I/R) injury has been verified by the fact that pharmacological or genetic stimulation of autophagy ameliorate the liver reperfusion injury^[643-645].

I/R impairs hepatocellular autophagy^[646] through I/R-induced ATP depletion leading to energy shortage and malfunction of the autophagic machinery. Moreover Ca²⁺ overloading during I/R results in calpain overproduction and ultimate loss of key autophagy proteins like Atg7. Interestingly the autophagy suppressor chloroquine attenuated liver injury when administered in early phases of I/R but aggravated the lesions, as expected, when given in late phases^[647].

Hepatic encephalopathy

Ammonia is an important mediator of hepatic encephalopathy. Increased ammonia levels rapidly induce an autophagic response that preferentially targets mitophagy^[648-650]. Ammonia induced autophagy may in fact be a protective mechanism against encephalopathy as suggested by a recent report. Deletion of Atg7 or loss of functional TFEB deteriorated ammonia detoxification in mice. By contrast activation of liver autophagy either by rapamycin administration or genetic TFEB expression reduced ammonia levels in acquired hyperammonaemia^[651].

Autoimmune hepatitis

The role of autophagy in autoimmune hepatitis (AIH) has not been adequately studied. It is suggested that autophagy is implicated in AIH through its involvement in antigen processing and presentation to T cells^[652] and its well proven role in liver fibrosis^[653], but the exact pathways have not been delineated.

Concanavalin A-induced hepatitis is an extensively used model for immune-mediated liver injury. Comparative proteomic results in this model have shown that the activation of immune system resulted in hepatitis with deregulation of autophagy as indicated by an increase in p62 and LC3B. Arctigenin is a biologically active lignan with antioxidant and anti-inflammatory properties. Pretreatment with arctigenin alleviated autophagy as well as apoptosis verifying that immunity and autophagy are interconnected in AIH pathogenesis^[654].

A group of researchers recently used the same model of concanavalin (conA) induced experimental hepatitis to clarify the role of autophagy in AIH. Methyl prednisolone (MP) treatment significantly decreased inflammation in the liver and activated the Akt/mTOR pathway to inhibit hepatocyte apoptosis and autophagy. Reduced numbers of autophagosomes were present in the MP treated group compared to the conA group. It was further shown that MP attenuated the mitochondria-mediated autophagy and apoptosis^[655]. In a second report on the same experimental model, accumulation of mature conventional dendritic cells (cDCs) was observed in the liver. *In vitro*, ConA treatment induced the expression of autophagy proteins and the formation of autophagosomes in dendritic cells. A further blockade of autophagy flux inhibited the maturation of DCs and the proliferation and differentiation of CD4⁺ T cells when ConA-induced DCs were co-cultured with CD4⁺ T cells. Taken together these studies elegantly showed that autophagy is critically implicated in AIH and aberrant autophagy and defective maturation of cDCs are involved in AIH immunopathogenesis^[656].

A recent clinical study using immunohistochemistry in liver biopsy samples from chronic HCV and AIH patients confirmed the central role of autophagy in AIH. Activated but impaired autophagy and less efficient elimination of damaged mitochondria were demonstrated in AIH as compared with HCV. Increased p62 levels significantly correlated with necroinflammation in AIH^[657].

Biliary disease

The mechanisms of liver damage in cholestasis are incompletely understood. Autophagy and protein degradation were shown to be impaired in cholestasis induced in bile duct ligated mice^[658-660]. Moreover, defective autophagy after chloroquine inhibition or deletion of Atg7 and Atg5 led to increased cholestatic liver injury^[661,662].

Accumulated toxic bile acids lead to ER stress, mitochondrial dysfunction with increased oxidative stress, inflammasome activation and apoptosis leading to liver fibrosis^[663]. These events should in fact activate autophagy in cholestasis but instead, at least in mice, it appears that autophagy is inhibited in cholestasis^[664,665]. Bile acids can inhibit autophagy in mice either *via* the farnesoid X receptor (FXR) during the feeding-fasting cycle^[114,115] or independently of FXR^[666]. How autophagy is affected in human cholestasis is under investigation.

In human disease autophagy was initially associated with the pathogenesis of primary biliary cholangitis (PBC)^[667-669]. As mentioned before autophagy is also involved in the processing and presentation of various antigens. It is only logical therefore that an interesting hypothesis implicating deregulated cholangiocyte autophagy connected to cholangiocyte senescence has been proposed to explain not only the pathogenesis of PBC but of the other fibrosing cholangiopathies including primary sclerosing cholangitis (PSC) and biliary atresia as well^[670].

An upregulation of autophagy was reported along with senescence in PBC^[668,671]. LC3B and p62 proteins were accumulated in damaged bile ductular cells in association with senescence markers^[68,125] suggesting that autophagy could induce and facilitate cholangiocyte senescence^[664,665,671-674]. Mitophagy may be specifically involved in PBC as granular expression of the mitochondrial protein PDC-E2 was co-localized with LC3^[667].

Autophagy has also been implicated in the treatment of PBC. Ursodeoxycholic acid (UDCA) is still the first line treatment of PBC while obeticholic acid (OCA) is a second-line treatment^[675-677]. Hydrophobic bile acids, such as glycochenodeoxycholic acid impair autophagy *in vitro* and induce abnormal expression of mitochondrial antigens and cellular senescence in cholangiocytes, possibly through induction of ER stress. Pretreatment with UDCA reduced ER stress and partially restored deregulated autophagy and cellular senescence^[678]. It is not clear how UDCA stimulates autophagy.

UDCA has been reported to be an FXR antagonist^[679] but this may not be the explanation^[680]. On the contrary, OCA is a semi-synthetic FXR agonist with anti-cholestatic functions including the suppression of endogenous bile acid synthesis and interference with hepatocellular bile acid transporter systems^[681]. OCA impairs autophagic flux *in vitro* and also *in vivo*. A favorable effect of treatment with OCA in a cholestatic disease like PBC would be incompatible with data, indicating that cholestasis progresses when autophagy is blocked^[661,662]. However, the other potent, anti-cholestatic properties of OCA can overcome the negative effects of reduced autophagy.

A recent paper offers an interesting explanation. Autophagy seems to be also impaired in human cholestatic conditions where accumulated bile acids induce Rubicon in an FXR-dependent fashion. Rubicon induction suppresses autophagosome-lysosome fusion and inhibits proper autophagolytic breakdown. Rubicon was also induced after treatment with the FXR agonist OCA. Genetic inhibition of Rubicon reversed the impairment of autophagic flux. In contrast, UDCA reduced Rubicon levels, enhanced autophagic flux and autophagolysosome formation independently of FXR^[680].

An overview of autophagy abnormalities is presented in [Table 1](#).

CONCLUSION

Autophagy is an important process through which intracellular parts are degraded in the lysosomes. It is a fine example of effective cellular recycling mechanism, connecting cellular quality control with energy saves. There are three types of autophagy with various pathways of delivery to the lysosomes: Macroautophagy (which is further divided into non selective autophagy and selective macroautophagy targeting special organelles or specific compounds for degradation), microautophagy and chaperon-mediated autophagy. Autophagy is related to major physiologic processes as cell death, inflammation and immunity. It is increasingly recognized that it is implicated in almost every aspect of liver diseases, and this can be the basis for future pathophysiologically based and targeted management.

Table 1 Overview of autophagy abnormalities in liver disease

Disease	Abnormalities of autophagy	Results	Ref.
Obesity	↓Autophagy; Hepatocytes: ↓Mitophagy, ↓Lipophagy; HSCs: ↓Autophagy	↑ER stress, →↑Lipids, ↑Insuline resistance, → Anti-fibrotic	Liu <i>et al</i> ^[203] , Lavallard <i>et al</i> ^[204] , Gual <i>et al</i> ^[205] , Tremblay <i>et al</i> ^[206]
NAFLD	↓Lipophagy; ↓CMA	Lipotoxicity, ↑Lipogenic enzymes	Madrigal-Matute <i>et al</i> ^[30] , Zhou <i>et al</i> ^[234] , Niso-Santano <i>et al</i> ^[235] , Singh <i>et al</i> ^[236]
NASH	Hepatocytes: ↓Autophagy, ↓Mitophagy; Kupffer cells: ↓Autophagy; LSECs: ↓Autophagy	↑Mallory-Denk bodies, ↑Inflammasome activation; ↑Cathepsins B,D, ↑M1 polarization, ↓M2 polarization; ↑Inflammation, fibrosis	Xu <i>et al</i> ^[272] , Nouredin <i>et al</i> ^[277] , Zhang <i>et al</i> ^[285] , Dey <i>et al</i> ^[287]
Alcoholic liver disease	Acute ETOH administration: ↑Autophagy, ↑Mitophagy, ↑Lipophagy, ↑Proteophagy; Chronic ETOH administration: ↑Autophagy (low dose), ↓Autophagy (high dose); Kupffer cells: ↓Autophagy, ↑Autophagy; HSCs: ↓Autophagy, ↑Autophagy	Protection, protection, protection, →Clearance of Mallory-Denk bodies; →Protection, →Mitochondrial damage, Cell death; Liver damage, protection; Reduced fibrosis, increased fibrosis	Chao <i>et al</i> ^[308] , Komatsu <i>et al</i> ^[311] , Yan <i>et al</i> ^[314] , Harada <i>et al</i> ^[318]
HBV	↑Autophagy, ↓Lysosomal acidification, ↑Mitophagy	↑Virus replication, ↓HBV degradation	Li <i>et al</i> ^[356] , Tang <i>et al</i> ^[357] , Luo <i>et al</i> ^[372] , Wang <i>et al</i> ^[383]
HCV	↑Autophagy, ↓Lipophagy, ↑Mitophagy; ↑CMA	↑Virus replication, steatosis, ↑Virus replication, ↓Apoptosis, persitent infection, ↑Virus replication	Ferraris <i>et al</i> ^[387] , Paul <i>et al</i> ^[395] , Jassey <i>et al</i> ^[404] , Ren <i>et al</i> ^[406]
Fibrosis-Cirrhosis	Hepatocytes: ↓Autophagy, ↓Lipophagy; Kupffer cells: ↓Mitophagy, or, ↑↑Mitophagy; HSCs: ↓Mitophagy, ↓Lipophagy, or, ↑Lipophagy, ↑Mitophagy; LSECs: ↑↓Autophagy; Ductular reaction: ↑Autophagy	↑Fibrosis, ↑Lipotoxicity, ↓TGFb, ↓Fibrosis; ↑TGFb, ↑Fibrosis; Pro-inflammatory anti-fibrotic: →Pro-fibrotic, →Pro-fibrotic, ↑Fibrosis, ↑Fibrosis	Zhang <i>et al</i> ^[437] , Singh <i>et al</i> ^[438] , Li <i>et al</i> ^[448] , Sun <i>et al</i> ^[463]
HCC, “Double edge sword”	Induction stage: ↑CMA, ↑Autophagy; Late stages: ↑Autophagy, or, ↓Autophagy, ↑Mitophagy, ↑Lipophagy	Anti-oncogenic: ↓YAP1, ↓proliferation, ↑Apoptosis→Anti-oncogenic, ↓Tumor suppressors; ↑Tumor progression, ↓↑Progression↑↓Progression	Wang <i>et al</i> ^[558] , Zhao <i>et al</i> ^[559] , Prieto-Domínguez <i>et al</i> ^[560] ; Nitire <i>et al</i> ^[544] , Yang <i>et al</i> ^[547] , Lin <i>et al</i> ^[549] , Chen <i>et al</i> ^[550] , Chen <i>et al</i> ^[551]
Cholangiocarcinoma	↑Autophagy	↑Tumor progression	Marciniak <i>et al</i> ^[580] , Teckman <i>et al</i> ^[581]
A1 antitrypsin deficiency	↓Autophagy		Yamamura <i>et al</i> ^[590] , Pastore <i>et al</i> ^[592]
Fibrinogen storage disease	↓Autophagy		Hu <i>et al</i> ^[609]
Wilson’S disease	↓Autophagy		Oami <i>et al</i> ^[611]
Glycogen storage disease	↓Autophagy		Xing <i>et al</i> ^[613]
Sepsis	Kupffer cells: ↑Autophagy, ↑↑Autophagy, ↓Mitophagy	M2 polarization, ↓Inflammasome activation; Kupffer cell apoptosis→Cytokine storm, ↓Apoptosis of CD4+ve T cells	Ying <i>et al</i> ^[615] , Neumann <i>et al</i> ^[616] , Sun <i>et al</i> ^[628] , Shan <i>et al</i> ^[629]
Acetaminophene liver damage	↓Autophagy, ↓Mitophagy, ↑Kupffer cell autophagy	↑APAP-Protein adducts	Sydor <i>et al</i> ^[618] , Kim <i>et al</i> ^[643] , Biel <i>et al</i> ^[644]
Acute liver failure	↑Autophagy, ↓Autophagy, ↓HSCs Mitophagy	HMGB1→HSCs activation (protective); ↑NO,ROS→↓HSCs→Devastation	Cheong <i>et al</i> ^[649] , Sridhar <i>et al</i> ^[652]
Ischemia/reperfusion injury	↓Autophagy		Kwak <i>et al</i> ^[658] , Huang <i>et al</i> ^[659]

Hepatic encephalopathy	↑Autophagy (NH4)	Protection	Woolbright <i>et al</i> ^[663] , Manley <i>et al</i> ^[666]
Autoimmune hepatitis	↑Autophagy, ↓ Mitophagy	Defective maturation of dendritic cells	Sasaki <i>et al</i> ^[671] , Sasaki <i>et al</i> ^[672] , Young <i>et al</i> ^[673]
Biliary disease (experimental)	↓Autophagy	Possibly through increased bile acids	Sasaki <i>et al</i> ^[665] , European Association for the Study of the Liver ^[675] , Lindor <i>et al</i> ^[676] , Panzitt <i>et al</i> ^[680]
Primary biliary cholangitis	Deregulated autophagy	Cholangiocyte senescence	Van de Graaf <i>et al</i> ^[669] , Sasaki <i>et al</i> ^[665] , Sasaki <i>et al</i> ^[674]

Note the double edge sword behaviour of autophagy, particularly evident in hepatocellular carcinoma. Autophagy refers to macroautophagy. HSCs: Hepatic stellate cells; LSECs: Liver sinusoidal endothelial cells; CMA: Chaperone mediated autophagy; ER: Endoplasmic reticulum; ASH: Acute alcoholic hepatitis.

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