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**Cell-type specific role of autophagy in the liver and its implications in non-alcoholic fatty liver disease**

Raza S *et al*. Hepatic autophagy and NAFLD

Sana Raza, Sangam Rajak, Rajani Singh, Jin Zhou, Rohit A. Sinha, Amit Goel

**Sana Raza, Sangam Rajak, Rohit A. Sinha,** Department of Endocrinology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Uttar Pradesh, Lucknow 226014, India

**Rajani Singh, Amit Goel,** Department of Hepatology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Uttar Pradesh, Lucknow 226014, India

**Jin Zhou,** CVMD, Duke-NUS Medical School, Singapore 169857, Singapore

**Co-corresponding authors:** Rohit A. Sinha and Amit Goel.

**Author contributions:** Raza S and Sinha RA reviewed and analyzed the literature, and wrote the overall manuscript; Rajak S, Singh R, Zhou J collected and reviewed the literature; Sinha RA and Goel A contributed equally to the overall intellectual input, review of the literature, and approved the manuscript. These authors helped with the synthesis of information and were the primary point of contact during the publication process.

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**Corresponding author: Amit Goel, BSc, DNB, MBBS, MD, MNAMS, Professor,** Department of Hepatology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Raebareli Road, Lucknow-226014, Uttar Pradesh, India. agoel.ag@gmail.com

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**Abstract**

Autophagy, a cellular degradative process, has emerged as a key regulator of cellular energy production and stress mitigation. Dysregulated autophagy is a common phenomenon observed in several human diseases, and its restoration offers curative advantage. Non-alcoholic fatty liver disease (NAFLD), more recently renamed metabolic dysfunction-associated steatotic liver disease, is a major metabolic liver disease affecting almost 30% of the world population. Unfortunately, NAFLD has no pharmacological therapies available to date. Autophagy regulates several hepatic processes including lipid metabolism, inflammation, cellular integrity and cellular plasticity in both parenchymal (hepatocytes) and non-parenchymal cells (Kupffer cells, hepatic stellate cells and sinusoidal endothelial cells) with a profound impact on NAFLD progression. Understanding cell type-specific autophagy in the liver is essential in order to develop targeted treatments for liver diseases such as NAFLD. Modulating autophagy in specific cell types can have varying effects on liver function and pathology, making it a promising area of research for liver-related disorders. This review aims to summarize our present understanding of cell-type specific effects of autophagy and their implications in developing autophagy centric therapies for NAFLD.

**Key Words:** Autophagy; Non-alcoholic fatty liver disease; Hepatocytes; Macrophages; Hepatic stellate cells

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**Core Tip:** This review presents a succinct overview of the cell-specific distinct effects of autophagy modulation on hepatic pathophysiology and its implication on the progression of non-alcoholic fatty liver disease (NAFLD). The effects of autophagy alteration on hepatocyte lipid metabolism, macrophage polarization and hepatic stellate cell plasticity are reviewed and discussed with reference to NAFLD pathobiology.

**INTRODUCTION**

Non-alcoholic fatty liver disease (NAFLD) is a hepatic manifestation of metabolic syndrome and a risk factor for diabetes, cardiovascular ailments, and hepatocellular cancers[1-3]. It is classically defined as hepatic steatosis which has developed in individuals with no or moderate alcohol consumption. The initial clinical presentation of NAFLD involves benign steatosis that may progress to a more severe form of the disease termed non-alcoholic steatohepatitis (NASH)[4]. NASH is characterized by increased hepatocyte damage, hepatocyte ballooning, inflammation, and fibrosis[5]. Several factors including high calorie diets, sedentary lifestyle, gut-microbiome, and genetic predisposition, constitute a multiple-hit basis of the progression of benign steatosis to NASH in certain individuals[6,7]. NASH is one of the leading causes of liver transplants worldwide[5]. Presently, there are no approved drug therapies for NAFLD and NASH. As physical activity is a key determinant of metabolic control, lifestyle modifications remain the only available treatment so far[8]. Furthermore, the prevalence of NAFLD, which is currently > 30%, has increased significantly in the last ten years with a nearly 50% increase occurring between 1990-2006 to 2016-2019[2]. At the molecular level, the development of NAFLD involves pathological changes in several hepatic cells including hepatocytes, macrophages, hepatic stellate cells (HSCs), endothelial cells and cholangiocytes[9]. Intracellular changes in the cellular metabolism, mitochondrial energetics, organellar homeostasis, redox hormesis and epigenetic changes in cellular plasticity govern the tissue damage and inflammatory milieu observed during NAFLD progression[10-13].

Autophagy is a cellular quality control process which is activated in response to energy crisis and cellular stress[14-16]. Historically, the liver has been recognized as an organ with high autophagy activity and hepatocytes and Kupffer cells were the first cell types where the metabolic role of autophagy and lysosomes were discovered[17,18]. Autophagy serves as a key regulator of hepatocyte, lipid, and carbohydrate metabolism in the liver[19]. Similarly, autophagy in liver macrophages and HSCs differentially regulates their plasticity from a quiescent to activated phenotype[20]. In this review, we will describe the distinct roles of cell-type specific autophagy in hepatic physiology and its deregulation in NAFLD.

**AUTOPHAGY MECHANISMS**

The term autophagy means “self-digestion” and plays a pivotal role in maintaining cellular homeostasis by recycling damaged or unnecessary cellular components. Autophagy ensures cell survival and contributes to various physiological and pathological processes. To date, three types of autophagy have been described: macroautophagy, micro-autophagy, and chaperone-mediated autophagy (CMA)[21]. Autophagy involves subcellular membrane trafficking to sequester a portion of cytoplasmic constituents and organelles by a membrane-sac (termed the phagophore) to form a double-membrane structure termed the autophagosome. The autophagosome is then transported to the lysosome for bulk protein degradation (proteolysis) of the sequestered intracellular materials by the lysosomal hydrolases. The breakdown products are utilized as an internally derived source of energy. Autophagy may be adaptive or constitutive. Constitutive autophagy is a mechanism of ‘cellular housekeeping’ that involves the removal of damaged or senescent organelles and helps to preserve basal energy balance. However, adaptive autophagy is characterized by recycling of intracellular constituents (proteins, lipids, glycogens, and organelles) to fulfill energy requirements in the event of nutrient deficiency. CMA is a selective cellular process where specific proteins are targeted for degradation by lysosomes with the help of chaperone proteins.

Macro-autophagy (hereafter referred to as autophagy) is a highly orchestrated process that can be divided into several key stages: Initiation, elongation, maturation, and degradation. The coordinated activity of several regulatory components tightly regulates the process of autophagy from initiation to termination. Autophagy genes, often referred to as autophagy-related genes (*Atgs*), are a group of genes responsible for regulating and executing the autophagic process within cells[22]. More than 30 autophagy-related (*ATG*) proteins have been identified and characterized thus far. The autophagic process is initiated by a serine-threonine protein kinase, Unc-51 Like autophagy activating kinase 1 (ULK1)[23]. The mammalian target of rapamycin (mTOR) is a central regulator of cell growth and metabolism and is known to inhibit autophagy when active. In nutrient-rich conditions, mTOR is activated, preventing autophagy initiation by phosphorylating the autophagy-initiating complex, ULK1/2. This phosphorylation inhibits ULK1/2 and prevents autophagosome formation. In contrast, AMP kinase (AMPK) is a sensor of cellular energy status. When energy levels are low (*e.g.*, during nutrient deprivation or stress), AMPK is activated. Activated AMPK phosphorylates ULK1/2, relieving the inhibition imposed by mTOR and promoting autophagy initiation. Additionally, AMPK activation further stimulates autophagy by inhibiting mTOR directly and by activating transcription factors such as transcription factor EB (TFEB), which control the expression of *Atgs* and various lysosomal genes. When activated, TFEB promotes autophagy by enhancing the production of autophagy-related proteins and lysosome biogenesis[24].

The initiation phase is primarily governed by the mTOR and AMPK pathways. The ULK1/2 complex plays a central role in autophagy initiation and is comprised of ULK1, *ATG13*, *ATG101* and *FIP200*[25]. When mTOR is inhibited or AMPK is activated in response to nutrient deprivation or stress, ULK1 is activated by phosphorylation, and in turn, phosphorylates *ATG13* and *FIP200* to initiate the process of autophagosome formation[26]. Once initiated, autophagy proceeds through the elongation and maturation stages. Key proteins like autophagy-related protein 5 (*ATG5*) and *ATG12* form complexes that contribute to the elongation (expansion) of the isolation membrane, which eventually seals to form the autophagosome, a double-membraned vesicle that engulfs cellular cargo[27]. *ATG5* is part of a complex with *ATG12* and *ATG16L1*, which is crucial for elongation of the phagophore and closure of the autophagosome. *ATG8* or lipid-­conjugated microtubule-associated protein 1A/1B-light chain 3 (LC3-phosphatidylethanolamine), which is lipidated and incorporated into the autophagosomal membranes, plays a central role in the biogenesis and elongation of autophagosomes[28].

The autophagy receptor or adaptor proteins facilitate the tethering of target proteins and organelles destined for degradation on to the autophagosome. Sequestosome­1, also known as p62/SQSTM1 is a cargo receptor that recognizes ubiquitinated cargo, such as damaged organelles or proteins, and targets them for selective autophagic degradation. P62 contains LC3-interacting regions to interact with LC3 on the autophagosome membrane. Once the double-membrane vesicle is formed, it travels along the microtubules to the lysosome, where the outer membrane of the autophagosome fuses with lysosomes *via* the interaction of a synaptosome complex containing STX17, SNAP29, RAB7, and VAMP8 with LAMP1 on the lysosome[28]. Inside the autolysosomes, the lysosomal enzymes enable the degradation of the cargo.

**AUTOPHAGY IN NAFLD**

NAFLD is characterized by the accumulation of excess fat (triglycerides) in the liver, independent from excessive alcohol consumption. Demonstration that autophagy plays a significant role in the pathogenesis of NAFLD comes from several lines of evidence described below:

***ATG gene knockout mouse models***

Studies performed in liver-specific autophagy gene (*ATG5* and *ATG7)* knockouts revealed a lipolytic role of autophagy, and mice deficient in either of these genes showed increased hepatic steatosis[29]. The loss of autophagy genes also increased hepatocyte susceptibility to gut endotoxin-induced injury[30]. Autophagy is also known to regulate hepatic inflammation. In this regard, hepatic macrophages also known as Kupffer cells derived from *ATG5-/-* mice fed with a high-fat diet (HFD), developed a pro-inflammatory phenotype resulting from macrophage polarization[31].

***Studies involving pharmacological/non-pharmacological autophagy inducers in animal models of NAFLD***

Preclinical experiments performed with a classical autophagy inducer, such as, rapamycin resulted in the reduction of hepatic steatosis and injury in animals fed a HFD[32]. Similarly, the administration of autophagy inducing hormones such as thyroid hormone, ghrelin, glucagon like peptide-1 and vitamin D also increased autophagy in mouse liver and reduced steatosis in animals fed high calorie diets[33-38]. In addition, several natural compounds including caffeine, epigallocatechin gallate, and resveratrol, together with several herbal extracts derived from traditional Chinese and Indian medicines, have exhibited potent pro-autophagy activity which is associated with their anti-NAFLD effect in animals[39-49]. Besides pharmacological agents, lifestyle modifications including intermittent fasting[50,51] and exercise[52-54] also induce hepatic autophagy as a means to delay and/or reduce NAFLD/NASH progression.

***Analysis of liver autophagy in human NAFLD***

Assessment of autophagy in the liver biopsies of patients with progressive degree of severity showed impaired autophagy characterized by reduced expression of lysosomal cathepsins, accumulation of p62 and decreased autophagy flux[55,56]. Furthermore, the impairment of autophagy strongly correlated with markers of hepatic injury and inflammation[55,56]. More recently, whole exome sequencing data has revealed pathogenic mutations in human autophagy-related genes which increases susceptibility to NAFLD development[57,58]. Notably, the defects in autophagy observed in human NAFLD are similar to that observed in murine models of NAFLD, in which an early increase in autophagic flux is followed by a late block in autophagic flux and a concomitant increase in endoplasmic reticulum (ER)-stress[56,59].

**AUTOPHAGY IN HEPATOCYTES**

Hepatocytes are cells of parenchymal origin, and are the metabolic hub of the liver. These are the primary functional cells of the liver and play a central role in metabolic processes, detoxification, and protein secretion. Not surprisingly, autophagy has been widely studied in these cells under physiological and pathological conditions including NAFLD. Hepatocytes rely on autophagy to remove damaged organelles, manage energy balance, and regulate lipid metabolism. The biological effects of autophagy on hepatocytes and its modulation under NAFLD are described below.

***Role of autophagy in hepatocyte lipid and carbohydrate metabolism***

Hepatocytes store excess neutral lipids in the form of lipid droplets (LDs) which are composed of triacylglycerol (TAG). These TAG stores can be degraded by lipases to release free fatty acids (FFAs) as fuel for ATP production. The lipolysis of TAGs mediated by an autophagy-lysosomal pathway was termed “lipophagy” in hepatocytes undergoing starvation[29]. The sequence of events involved in lipophagy consists of the engulfment of LDs by the autophagosomes, followed by their fusion with lysosomes where lipolysis of TAG takes place. The FFAs released from the lysosomes can then be utilized for mitochondrial fat oxidation[29]. The key lipase involved in this process is known as lysosomal lipase[29]. Defects in hepatocyte lipophagy are suspected to be a major cause of early NAFLD development in humans[60-62]. In addition to lipophagy, CMA also plays a key role in the lipolysis of TAGs within hepatocytes[63]. In this regard, both LD-associated proteins perilipin 2 and perilipin 3 have been identified as CMA substrates and their degradation *via* CMA precedes lipolysis by lipophagy[63]. Additionally, lipid degradation by microautophagy termed “macrolipophagy” has been reported to occur in mouse hepatocytes supplemented with oleate, followed by nutrient starvation[64]. Lipophagy has been shown to be activated by MTORC1 inhibition[65], fibroblast growth factor-21[36], as well as by the activation of nuclear receptors including thyroid hormone receptors, peroxisome proliferator-activated receptor alpha and TFEB exhibiting anti-steatosis effects[47,66-69]. More recently, the induction of lipophagy was shown to enhance lysosomal mediated lipid exocytosis, thereby ameliorating NASH in animal models[70].

Surprisingly, autophagy and autophagy genes have also been implicated in the assembly of TAGs in hepatocytes. Reports have shown that the loss of autophagy genes such as *MAP1LC3*[71], *ATG7*[72] and *FIP200*[30] leads to decreased LD accumulation in hepatocytes (Figure 1). This opposing effect by autophagy, as described above suggests paradoxical dual roles of autophagy in LD assembly *vs* degradation which may be due to the differential effects of *ATG* genes and nutrient status in cells[73].

Besides its role in lipid metabolism, autophagy also plays a significant role in hepatocyte carbohydrate metabolism by regulating glycogen breakdown[74]. The lysosomal α-acid glucosidase can hydrolyze glycogen and release free glucose[75]. Excessive glycogen deposition in hepatocytes commonly coexists with hepatic injury in both patients with NAFLD[76] and those with glycogen storage disease type Ia (GSD Ia)[77]. GSD Ia is the most common glycogen storage disease. It is caused by the loss-of-function mutation of glucose-6-phosphatase, the enzyme converting glucose-6-phosphate to free glucose. Besides glycogen, GSD Ia is also characterized by excess lipid accumulation in the liver, and is now considered a fatty liver-like disease. Recently, the induction of autophagy was shown to attenuate the development of hepatic steatosis and reduce glycogen content in an animal model of GSD Ia[78]. These results, therefore, suggest an intricate interplay between hepatocyte autophagy and glycogenolysis.

***Autophagy and hepatocyte lipotoxicity***

Lee *et al*[79] used the term “Lipotoxicity” for the first time to describe the harmful effects of lipid species such as saturated FFAs (SFAs) and cholesterol in non-adipose organs. At the molecular level, NAFLD/NASH induced lipotoxicity in hepatocytes is characterized by increased oxidative stress, mitochondrial dysfunction, impaired unfolded protein response (UPR), pro-inflammatory cytokine production, and cell death[80,81]. Intriguingly, basal autophagy inhibition is also observed in response to SFAs such as palmitic acids[82]. Chronic SFAs administration impairs autophagosomal-lysosomal fusion, causes disruption of hepatocyte autophagy through suppression of the immune surveillance protein DDX58/Rig-1 (DExD/H box helicase) and stimulates the STING-MTORC1 pathway contributing to the autophagy inhibition reported in advanced NAFLD[65,82,83]. Therefore, restoration autophagic flux has emerged as an important strategy to counter lipotoxicity in hepatocytes[84].

In addition to being involved in macromolecular breakdown of lipids, proteins and carbohydrates, autophagy is also involved in selective removal of damaged organelles. The autophagic removal of mitochondria, known as “mitophagy” is a process of mitochondrial pruning that prevents the accumulation of damaged mitochondria resulting from increased oxidative stress[85]. Defective mitophagy has been shown to be associated with impaired mitochondrial β-oxidation and increased oxidative stress and lipoapoptosis in both animal models as well as in human NAFLD[86,87]. In hepatocytes, the accumulation of damaged mitochondria resulting from lipotoxicity, may lead to mitochondrial mediated apoptosis as well as activation of the inflammasome complex[88]. Therefore, the induction of mitophagy ensures both sustained mitochondrial energetics as well as cell survival (Figure 1). Several mechanisms have been proposed to regulate mitophagy in NAFLD[35,88-96]. Acyl coenzyme A: lysocardiolipin acyltransferase-1 expression was shown to be elevated in HFD fed mice, and its silencing restored mitophagy in isolated hepatocytes with observable improvement in mitochondrial architecture and reduced hepatic steatosis in mice[97]. Furthermore, the plant flavanol quercetin alleviates HFD-induced hepatic steatosis by activating AMPK-dependent mitophagy[98]. Furthermore, sirtuin 3 overexpression stimulates mitophagy and protects hepatic cells against palmitic acid-induced oxidative stress[99]. Mitophagy is also induced by thyroid hormone[100] through increased reactive oxygen species (ROS) production from mitochondria, the release of intracellular calcium, and activation of calcium/calmodulin-dependent protein kinase kinase and AMPK to both maintain mitochondrial fat oxidation as well as prevent further cell damage by ROS.

Autophagy also protects hepatocytes against lipotoxicity-induced oxidative stress by degrading Kelch like ECH associated protein 1 (KEAP1), which results in nuclear factor, erythroid 2 Like 2 (NRF2/NFE2L2) nuclear translocation and transcription of antioxidant genes[101]. Autophagy gene ULK1 was shown to enhance the interaction of autophagy adapter protein p62/SQSTM1 with KEAP1 which results in the autophagy-mediated degradation of KEAP1 and NRF2 mediated protection from lipotoxicity (Figure 1)[102].

SFA-induced ER-stress and impaired UPR response also are key features associated with NAFLD progression in humans[56,103]. SFAs, cause ER stress by increasing saturated diacyl glycerolipid and saturated phospholipid accumulation in the ER, which causes persistent inositol-requiring enzyme-1α, and protein kinase RNA-like ER kinase activation in hepatocytes[104,105]. Eventually SFA-induced hepatocyte lipoapoptosis occurs owing to continuous UPR activation, which results in Jun N-terminal kinase and C/EBP Homologous Protein-mediated overexpression of proapoptotic proteins such as p53 upregulated modulator of apoptosis[106]. Autophagy serves as a key degradative mechanism for misfolded proteins in hepatocytes thus alleviating ER-stress caused by SFAs[107]. In this regard, HFD feeding was associated with increased hepatic ER stress and insulin resistance in autophagy defective animals[108]. Surprisingly, rescue experiments with *ATG7* gene overexpression dramatically relieved lipid-induced ER-stress in the mouse liver, as well as hepatic insulin sensitivity[108]. Besides degrading specific misfolded proteins, autophagy can also degrade parts of damaged ER by a process known as “ER-Phagy”. Although the mechanistic basis of this process is still not very clear in hepatocytes, its role in NAFLD pathogenesis was highlighted by RNA sequencing data revealing numerous ER-phagy receptors such as ATL3, SEC62, and RTN3 which were differentially regulated in patients with NAFLD/NASH[107]. These data point towards ER-phagy playing an essential role during NASH and underscores its importance as a possible novel strategy for NASH treatment.

SFA exposure in hepatocytes triggers the NLRP3-inflammasone signaling, leading to the activation of interleukin (IL)-1β which causes hepatocyte cell death[109-112]. The inhibition of inflammasome activation and hepatocyte pyroptosis is another way of cellular protection conferred by autophagy in hepatocytes[35].

**AUTOPHAGY IN LIVER MACROPHAGES**

The liver is a vital organ with diverse functions, including metabolism, detoxification, and immune regulation. Within the liver’s intricate cellular landscape, Kupffer cells, the resident macrophages, are critical players in immune surveillance and tissue homeostasis. Autophagy, a conserved intracellular process, has emerged as a key regulator of Kupffer cell functions and liver physiology. Autophagy in Kupffer cells, plays a pivotal role in maintaining hepatic homeostasis, regulating inflammation, by eliminating misfolded or aggregated proteins, removing damaged organelles and invading pathogens[113].

Macrophages are highly heterogeneous immune cells, which can polarize to diverse phenotypes in response to the surrounding microenvironment[114]. During inflammation or injury, macrophage polarization determines the fate of an organ[114]. When an organ or a tissue is inflicted with an infection or injury, macrophages are first polarized to their pro-inflammatory M1 phenotype to facilitate the removal of antigens and necrotic cells by releasing pro-inflammatory cytokines. Furthermore, the M1 macrophages polarize with the M2 macrophages at the stage of repair, to secrete anti-inflammatory cytokines and suppress inflammation, which promotes tissue repair and remodeling. Autophagy regulates macrophage polarization in NAFLD[31,115,116]. Macrophage autophagy reduces chronic inflammation and lowers the progression of organ fibrosis by inhibiting M1 macrophage polarization[117] (Figure 1). Impaired macrophage autophagy increased immune response and chronic hepatic inflammation and injury in obese mice[31]. Ubiquitin-specific protease 19-induced macrophage autophagy promoted anti-inflammatory M2-like macrophage polarization[116]. Chronic liver injury results in organ scarring, termed liver fibrosis. Tissue-resident macrophages are the crucial regulators of organ fibrosis[118]. Inflammation plays a vital role and may be a cause of fibrosis[119]. As macrophage autophagy inhibits macrophage polarization to pro-inflammatory M1 type, it may be a potential target for organ fibrosis. Macrophage activation and polarization are increasingly being recognized to play an essential role in liver inflammation and fibrosis[120]. Autophagy inhibited the release of inflammatory cytokines, particularly IL-1, from hepatic macrophages and reduced HSC activation to protect against liver fibrosis in mice[121]. Also, the suppression of Atg5 showed increased liver inflammation and fibrosis *via* the enhanced mitochondrial ROS/NF-κB/IL-1α/β pathway in autophagy-deficient liver macrophages[122]. Macrophage autophagy was reported to downregulate hepatic inflammation by inhibiting inflammasome-dependent IL-1β production[123]. Spermine, a polyamine, reduced liver injury by inhibiting the pro-inflammatory response of liver-resident macrophages by inducing autophagy[124]. LC3-associated phagocytosis (LAP) inhibited inflammation and liver fibrosis by pharmacological as well as genetic interventions. Inhibition of LAP aggravated the pro-inflammatory and pro-fibrotic phenotype in the liver[125]. Autophagy is also involved in immune regulation in liver macrophages. It promotes antigen presentation and major histocompatibility complex-II expression, facilitating efficient antigen recognition by T cells. Conversely, defective autophagy can lead to exaggerated inflammatory responses[126]. Dysregulation of autophagy in Kupffer cells can have wide-ranging implications for liver diseases, making it an attractive target for future therapeutic interventions. Further research into the precise mechanisms and therapeutic potential of autophagy modulation in liver macrophages is warranted to advance our understanding of liver pathophysiology and develop novel treatment strategies.

**AUTOPHAGY IN HSCs**

Among several cell types that contribute to liver function and pathology, HSCs have emerged as key players in the development of liver fibrosis, a common endpoint in chronic liver diseases. Autophagy, a cellular process of self-digestion and recycling, has gained increasing attention due to its role in HSC biology and its implications in liver disease progression. Autophagy in HSCs is intricately involved in maintaining metabolic homeostasis. It ensures an efficient turnover of cellular components, provides energy during stress or activation, and helps regulate key signaling pathways. Dysregulation of autophagy in HSCs can disrupt these metabolic processes and contribute to liver fibrosis and disease progression.

Upon liver injury or inflammation, HSCs undergo activation, transforming into proliferative, fibrogenic myofibroblasts that contribute to fibrous scar formation[127]. The role of autophagy in HSC activation remains paradoxical and context specific. Studies performed in HSCs *in vitro* and *in vivo* showed the profibrotic effect of autophagy induction during transforming growth factor beta induced HSC activation[128] (Figure 1). Specifically, autophagy is proposed to induce the activation of HSCs through lipophagy, a selective type of autophagy that degrades LDs[129]. On the other hand, autophagy also plays a critical role in maintaining HSC quiescence and limiting their activation. Inhibition of autophagy in activated HSCs has been associated with increased fibrogenesis, while induction of autophagy can suppress their activation and collagen production[130] (Figure 1). Indeed, HSC autophagy attenuated liver fibrosis by inhibiting the release of extracellular vesicles[131]. Autophagy in HSCs was recently shown to induce the release of miR-29a. Inhibition of autophagy reduced miR-29a secretion and repressed fibrogenic gene expression in a mouse model of liver fibrosis and in patients with chronic hepatitis C infection[132]. These findings underscore the therapeutic potential of targeting autophagy in HSCs to mitigate liver fibrosis and, consequently, liver disease progression. Autophagy in HSCs has significant implications for liver disease. Understanding these mechanisms holds promise for developing targeted therapies to modulate HSC metabolism and mitigate liver fibrosis. The role of autophagy in maintaining HSC quiescence and limiting fibrogenesis makes it a promising target for therapeutic intervention. Pharmacological agents that regulate autophagy in HSCs are being investigated for their potential to halt or reverse liver fibrosis and alleviate the burden of liver diseases worldwide. Furthermore, strategies to enhance the specificity of these interventions to HSCs also hold promise for minimizing their off-target effects.

***Autophagy in liver sinusoidal endothelial cells (LSECs)***

LSECs form the first barrier of defense in the liver owing to their unique position, lining the sinusoidal lumen. Endothelial dysfunction is known to play a key role in liver injury[133]. Autophagy maintains cellular integrity, phenotype and homeostasis and can be found in various cell types, including liver endothelial cells[134]. Decreased autophagy has been observed in liver endothelial cells of patients with NASH as compared to patients with simple steatosis or those with normal liver[135]. The selective disruption of *ATG5* or *ATG7* in endothelial cells impairs the normal endothelial phenotype and favors liver injury, inflammation and fibrosis in mice exposed to prolonged HFD feeding or carbon tetrachloride[133,135] (Figure 1).

**CONCLUSION**

Autophagy in the liver plays key role in hepatic metabolism, immunomodulation, and cellular plasticity with profound effects on NAFLD progression. Future research should focus on better understanding the role of autophagy in inter-cellular crosstalk among various cell types of the liver and its targeting as a future therapy for NAFLD/NASH in humans. Investigating hepatocyte-specific autophagy mechanisms and their response to various stressors, such as nutrient imbalances, oxidative stress, and toxic insults, is crucial to explore the therapeutic potential of autophagy modulation in NAFLD/NASH. Understanding how autophagy affects inflammation and antigen presentation in Kupffer cells could provide insights into liver-related immune disorders and manipulating autophagy in these cells may have implications for treating conditions like liver fibrosis. Additionally, exploring how autophagy contributes to LSEC integrity, angiogenesis, and regulation of blood flow may provide a better understanding of its role in liver health and disease. Furthermore, the deduction of molecular mechanisms by which autophagy influences HSC activation and collagen production can provide insights into therapeutic strategies for liver fibrosis.

Given the dynamic sequence of involvement of different cell types and the pleiotropic effect of autophagy during NAFLD progression, an optimal therapeutic time-window for targeting autophagy should be identified. Finally, identifying biomarkers of autophagy flux in humans would be useful clinically to monitor disease progression and response to treatment. Clinical trials of autophagy modulating drugs for NAFLD/NASH treatment could provide significant therapeutic advances, particularly since there are no pharmacological treatments for this disease.

**REFERENCES**

1 **Llovet JM**, Willoughby CE, Singal AG, Greten TF, Heikenwälder M, El-Serag HB, Finn RS, Friedman SL. Nonalcoholic steatohepatitis-related hepatocellular carcinoma: pathogenesis and treatment. *Nat Rev Gastroenterol Hepatol* 2023; **20**: 487-503 [PMID: 36932227 DOI: 10.1038/s41575-023-00754-7]

2 **Wong VW**, Ekstedt M, Wong GL, Hagström H. Changing epidemiology, global trends and implications for outcomes of NAFLD. *J Hepatol* 2023; **79**: 842-852 [PMID: 37169151 DOI: 10.1016/j.jhep.2023.04.036]

3 **Raza S**, Rajak S, Anjum B, Sinha RA. Molecular links between non-alcoholic fatty liver disease and hepatocellular carcinoma. *Hepatoma Res* 2019; **5**: 42 [PMID: 31867441 DOI: 10.20517/2394-5079.2019.014]

4 **Pierantonelli I**, Svegliati-Baroni G. Nonalcoholic Fatty Liver Disease: Basic Pathogenetic Mechanisms in the Progression From NAFLD to NASH. *Transplantation* 2019; **103**: e1-e13 [PMID: 30300287 DOI: 10.1097/TP.0000000000002480]

5 **Kanwal F**, Shubrook JH, Younossi Z, Natarajan Y, Bugianesi E, Rinella ME, Harrison SA, Mantzoros C, Pfotenhauer K, Klein S, Eckel RH, Kruger D, El-Serag H, Cusi K. Preparing for the NASH Epidemic: A Call to Action. *Gastroenterology* 2021; **161**: 1030-1042.e8 [PMID: 34416976 DOI: 10.1053/j.gastro.2021.04.074]

6 **Okekunle AP**, Youn J, Song S, Chung GE, Yang SY, Kim YS, Lee JE. Predicted pro-inflammatory hs-CRP score and non-alcoholic fatty liver disease. *Gastroenterol Rep (Oxf)* 2023; **11**: goad059 [PMID: 37842198 DOI: 10.1093/gastro/goad059]

7 **Fang YL**, Chen H, Wang CL, Liang L. Pathogenesis of non-alcoholic fatty liver disease in children and adolescence: From "two hit theory" to "multiple hit model". *World J Gastroenterol* 2018; **24**: 2974-2983 [PMID: 30038464 DOI: 10.3748/wjg.v24.i27.2974]

8 **Raza S**, Rajak S, Upadhyay A, Tewari A, Anthony Sinha R. Current treatment paradigms and emerging therapies for NAFLD/NASH. *Front Biosci (Landmark Ed)* 2021; **26**: 206-237 [PMID: 33049668 DOI: 10.2741/4892]

9 **Park HJ**, Choi J, Kim H, Yang DY, An TH, Lee EW, Han BS, Lee SC, Kim WK, Bae KH, Oh KJ. Cellular heterogeneity and plasticity during NAFLD progression. *Front Mol Biosci* 2023; **10**: 1221669 [PMID: 37635938 DOI: 10.3389/fmolb.2023.1221669]

10 **Eslam M**, Valenti L, Romeo S. Genetics and epigenetics of NAFLD and NASH: Clinical impact. *J Hepatol* 2018; **68**: 268-279 [PMID: 29122391 DOI: 10.1016/j.jhep.2017.09.003]

11 **Chakravarthy MV**, Neuschwander-Tetri BA. The metabolic basis of nonalcoholic steatohepatitis. *Endocrinol Diabetes Metab* 2020; **3**: e00112 [PMID: 33102794 DOI: 10.1002/edm2.112]

12 **Kim YS**, Kim SG. Endoplasmic reticulum stress and autophagy dysregulation in alcoholic and non-alcoholic liver diseases. *Clin Mol Hepatol* 2020; **26**: 715-727 [PMID: 32951410 DOI: 10.3350/cmh.2020.0173]

13 **Prasun P**. Mitochondrial dysfunction in metabolic syndrome. *Biochim Biophys Acta Mol Basis Dis* 2020; **1866**: 165838 [PMID: 32428560 DOI: 10.1016/j.bbadis.2020.165838]

14 **Ueno T**, Komatsu M. Autophagy in the liver: functions in health and disease. *Nat Rev Gastroenterol Hepatol* 2017; **14**: 170-184 [PMID: 28053338 DOI: 10.1038/nrgastro.2016.185]

15 **Ke PY**. Diverse Functions of Autophagy in Liver Physiology and Liver Diseases. *Int J Mol Sci* 2019; **20** [PMID: 30642133 DOI: 10.3390/ijms20020300]

16 **Qian H**, Chao X, Williams J, Fulte S, Li T, Yang L, Ding WX. Autophagy in liver diseases: A review. *Mol Aspects Med* 2021; **82**: 100973 [PMID: 34120768 DOI: 10.1016/j.mam.2021.100973]

17 **Deter RL**, Baudhuin P, De Duve C. Participation of lysosomes in cellular autophagy induced in rat liver by glucagon. *J Cell Biol* 1967; **35**: C11-C16 [PMID: 6055998 DOI: 10.1083/jcb.35.2.c11]

18 **Hendy R**, Grasso P. Reversibility of lysosomal and glucose 6-phosphatase changes produced in the rat liver by dimethylnitrosamine. *Chem Biol Interact* 1975; **10**: 395-406 [PMID: 167989 DOI: 10.1016/0009-2797(75)90070-8]

19 **Kuramoto K**, He C. Degradative and Non-Degradative Roles of Autophagy Proteins in Metabolism and Metabolic Diseases. *Front Cell Dev Biol* 2022; **10**: 844481 [PMID: 35646940 DOI: 10.3389/fcell.2022.844481]

20 **Weiskirchen R**, Tacke F. Relevance of Autophagy in Parenchymal and Non-Parenchymal Liver Cells for Health and Disease. *Cells* 2019; **8** [PMID: 30609663 DOI: 10.3390/cells8010016]

21 **Wang L**, Klionsky DJ, Shen HM. The emerging mechanisms and functions of microautophagy. *Nat Rev Mol Cell Biol* 2023; **24**: 186-203 [PMID: 36097284 DOI: 10.1038/s41580-022-00529-z]

22 **Mizushima N**, Yoshimori T, Ohsumi Y. The role of Atg proteins in autophagosome formation. *Annu Rev Cell Dev Biol* 2011; **27**: 107-132 [PMID: 21801009 DOI: 10.1146/annurev-cellbio-092910-154005]

23 **Zachari M**, Ganley IG. The mammalian ULK1 complex and autophagy initiation. *Essays Biochem* 2017; **61**: 585-596 [PMID: 29233870 DOI: 10.1042/EBC20170021]

24 **Song TT**, Cai RS, Hu R, Xu YS, Qi BN, Xiong YA. The important role of TFEB in autophagy-lysosomal pathway and autophagy-related diseases: a systematic review. *Eur Rev Med Pharmacol Sci* 2021; **25**: 1641-1649 [PMID: 33629334 DOI: 10.26355/eurrev\_202102\_24875]

25 **Jung CH**, Jun CB, Ro SH, Kim YM, Otto NM, Cao J, Kundu M, Kim DH. ULK-Atg13-FIP200 complexes mediate mTOR signaling to the autophagy machinery. *Mol Biol Cell* 2009; **20**: 1992-2003 [PMID: 19225151 DOI: 10.1091/mbc.e08-12-1249]

26 **Chang YY**, Neufeld TP. An Atg1/Atg13 complex with multiple roles in TOR-mediated autophagy regulation. *Mol Biol Cell* 2009; **20**: 2004-2014 [PMID: 19225150 DOI: 10.1091/mbc.e08-12-1250]

27 **Mizushima N**, Noda T, Yoshimori T, Tanaka Y, Ishii T, George MD, Klionsky DJ, Ohsumi M, Ohsumi Y. A protein conjugation system essential for autophagy. *Nature* 1998; **395**: 395-398 [PMID: 9759731 DOI: 10.1038/26506]

28 **Kabeya Y**, Mizushima N, Ueno T, Yamamoto A, Kirisako T, Noda T, Kominami E, Ohsumi Y, Yoshimori T. LC3, a mammalian homologue of yeast Apg8p, is localized in autophagosome membranes after processing. *EMBO J* 2000; **19**: 5720-5728 [PMID: 11060023 DOI: 10.1093/emboj/19.21.5720]

29 **Singh R**, Kaushik S, Wang Y, Xiang Y, Novak I, Komatsu M, Tanaka K, Cuervo AM, Czaja MJ. Autophagy regulates lipid metabolism. *Nature* 2009; **458**: 1131-1135 [PMID: 19339967 DOI: 10.1038/nature07976]

30 **Ma D**, Molusky MM, Song J, Hu CR, Fang F, Rui C, Mathew AV, Pennathur S, Liu F, Cheng JX, Guan JL, Lin JD. Autophagy deficiency by hepatic FIP200 deletion uncouples steatosis from liver injury in NAFLD. *Mol Endocrinol* 2013; **27**: 1643-1654 [PMID: 23960084 DOI: 10.1210/me.2013-1153]

31 **Liu K**, Zhao E, Ilyas G, Lalazar G, Lin Y, Haseeb M, Tanaka KE, Czaja MJ. Impaired macrophage autophagy increases the immune response in obese mice by promoting proinflammatory macrophage polarization. *Autophagy* 2015; **11**: 271-284 [PMID: 25650776 DOI: 10.1080/15548627.2015.1009787]

32 **Lin CW**, Zhang H, Li M, Xiong X, Chen X, Chen X, Dong XC, Yin XM. Pharmacological promotion of autophagy alleviates steatosis and injury in alcoholic and non-alcoholic fatty liver conditions in mice. *J Hepatol* 2013; **58**: 993-999 [PMID: 23339953 DOI: 10.1016/j.jhep.2013.01.011]

33 **Sinha RA**, You SH, Zhou J, Siddique MM, Bay BH, Zhu X, Privalsky ML, Cheng SY, Stevens RD, Summers SA, Newgard CB, Lazar MA, Yen PM. Thyroid hormone stimulates hepatic lipid catabolism via activation of autophagy. *J Clin Invest* 2012; **122**: 2428-2438 [PMID: 22684107 DOI: 10.1172/JCI60580]

34 **Mao Y**, Cheng J, Yu F, Li H, Guo C, Fan X. Ghrelin Attenuated Lipotoxicity via Autophagy Induction and Nuclear Factor-κB Inhibition. *Cell Physiol Biochem* 2015; **37**: 563-576 [PMID: 26329041 DOI: 10.1159/000430377]

35 **Yu X**, Hao M, Liu Y, Ma X, Lin W, Xu Q, Zhou H, Shao N, Kuang H. Liraglutide ameliorates non-alcoholic steatohepatitis by inhibiting NLRP3 inflammasome and pyroptosis activation via mitophagy. *Eur J Pharmacol* 2019; **864**: 172715 [PMID: 31593687 DOI: 10.1016/j.ejphar.2019.172715]

36 **Byun S**, Seok S, Kim YC, Zhang Y, Yau P, Iwamori N, Xu HE, Ma J, Kemper B, Kemper JK. Fasting-induced FGF21 signaling activates hepatic autophagy and lipid degradation via JMJD3 histone demethylase. *Nat Commun* 2020; **11**: 807 [PMID: 32042044 DOI: 10.1038/s41467-020-14384-z]

37 **Raza S**, Tewari A, Rajak S, Sinha RA. Vitamins and non-alcoholic fatty liver disease: A Molecular Insight(\*). *Liver Res* 2021; **5**: 62-71 [PMID: 34221537 DOI: 10.1016/j.livres.2021.03.004]

38 **Tripathi M**, Singh BK, Zhou J, Tikno K, Widjaja A, Sandireddy R, Arul K, Abdul Ghani SAB, Bee GGB, Wong KA, Pei HJ, Shekeran SG, Sinha RA, Singh MK, Cook SA, Suzuki A, Lim TR, Cheah CC, Wang J, Xiao RP, Zhang X, Chow PKH, Yen PM. Vitamin B(12) and folate decrease inflammation and fibrosis in NASH by preventing syntaxin 17 homocysteinylation. *J Hepatol* 2022; **77**: 1246-1255 [PMID: 35820507 DOI: 10.1016/j.jhep.2022.06.033]

39 **Sinha RA**, Farah BL, Singh BK, Siddique MM, Li Y, Wu Y, Ilkayeva OR, Gooding J, Ching J, Zhou J, Martinez L, Xie S, Bay BH, Summers SA, Newgard CB, Yen PM. Caffeine stimulates hepatic lipid metabolism by the autophagy-lysosomal pathway in mice. *Hepatology* 2014; **59**: 1366-1380 [PMID: 23929677 DOI: 10.1002/hep.26667]

40 **Gong LL**, Li GR, Zhang W, Liu H, Lv YL, Han FF, Wan ZR, Shi MB, Liu LH. Akebia Saponin D Decreases Hepatic Steatosis through Autophagy Modulation. *J Pharmacol Exp Ther* 2016; **359**: 392-400 [PMID: 27672081 DOI: 10.1124/jpet.116.236562]

41 **Liu C**, Liao JZ, Li PY. Traditional Chinese herbal extracts inducing autophagy as a novel approach in therapy of nonalcoholic fatty liver disease. *World J Gastroenterol* 2017; **23**: 1964-1973 [PMID: 28373762 DOI: 10.3748/wjg.v23.i11.1964]

42 **Ding S**, Jiang J, Zhang G, Bu Y, Zhang G, Zhao X. Resveratrol and caloric restriction prevent hepatic steatosis by regulating SIRT1-autophagy pathway and alleviating endoplasmic reticulum stress in high-fat diet-fed rats. *PLoS One* 2017; **12**: e0183541 [PMID: 28817690 DOI: 10.1371/journal.pone.0183541]

43 **Wang H**, Zhu YY, Wang L, Teng T, Zhou M, Wang SG, Tian YZ, Du L, Yin XX, Sun Y. Mangiferin ameliorates fatty liver via modulation of autophagy and inflammation in high-fat-diet induced mice. *Biomed Pharmacother* 2017; **96**: 328-335 [PMID: 29024899 DOI: 10.1016/j.biopha.2017.10.022]

44 **Zhang L**, Yao Z, Ji G. Herbal Extracts and Natural Products in Alleviating Non-alcoholic Fatty Liver Disease via Activating Autophagy. *Front Pharmacol* 2018; **9**: 1459 [PMID: 30618753 DOI: 10.3389/fphar.2018.01459]

45 **Li T**, Wen L, Cheng B. Cordycepin alleviates hepatic lipid accumulation by inducing protective autophagy via PKA/mTOR pathway. *Biochem Biophys Res Commun* 2019; **516**: 632-638 [PMID: 31242974 DOI: 10.1016/j.bbrc.2019.06.108]

46 **Wang Y**, Zhao H, Li X, Wang Q, Yan M, Zhang H, Zhao T, Zhang N, Zhang P, Peng L, Li P. Formononetin alleviates hepatic steatosis by facilitating TFEB-mediated lysosome biogenesis and lipophagy. *J Nutr Biochem* 2019; **73**: 108214 [PMID: 31520816 DOI: 10.1016/j.jnutbio.2019.07.005]

47 **Zhou W**, Yan X, Zhai Y, Liu H, Guan L, Qiao Y, Jiang J, Peng L. Phillygenin ameliorates nonalcoholic fatty liver disease via TFEB-mediated lysosome biogenesis and lipophagy. *Phytomedicine* 2022; **103**: 154235 [PMID: 35716542 DOI: 10.1016/j.phymed.2022.154235]

48 **Shen B**, Wang Y, Cheng J, Peng Y, Zhang Q, Li Z, Zhao L, Deng X, Feng H. Pterostilbene alleviated NAFLD via AMPK/mTOR signaling pathways and autophagy by promoting Nrf2. *Phytomedicine* 2023; **109**: 154561 [PMID: 36610156 DOI: 10.1016/j.phymed.2022.154561]

49 **Yu H**, Yan S, Jin M, Wei Y, Zhao L, Cheng J, Ding L, Feng H. Aescin can alleviate NAFLD through Keap1-Nrf2 by activating antioxidant and autophagy. *Phytomedicine* 2023; **113**: 154746 [PMID: 36905866 DOI: 10.1016/j.phymed.2023.154746]

50 **Lavallee CM**, Bruno A, Ma C, Raman M. The Role of Intermittent Fasting in the Management of Nonalcoholic Fatty Liver Disease: A Narrative Review. *Nutrients* 2022; **14** [PMID: 36364915 DOI: 10.3390/nu14214655]

51 **Ma YN**, Jiang X, Tang W, Song P. Influence of intermittent fasting on autophagy in the liver. *Biosci Trends* 2023; **17**: 335-355 [PMID: 37661370 DOI: 10.5582/bst.2023.01207]

52 **Pi H**, Liu M, Xi Y, Chen M, Tian L, Xie J, Chen M, Wang Z, Yang M, Yu Z, Zhou Z, Gao F. Long-term exercise prevents hepatic steatosis: a novel role of FABP1 in regulation of autophagy-lysosomal machinery. *FASEB J* 2019; **33**: 11870-11883 [PMID: 31366243 DOI: 10.1096/fj.201900812R]

53 **Gao Y**, Zhang W, Zeng LQ, Bai H, Li J, Zhou J, Zhou GY, Fang CW, Wang F, Qin XJ. Exercise and dietary intervention ameliorate high-fat diet-induced NAFLD and liver aging by inducing lipophagy. *Redox Biol* 2020; **36**: 101635 [PMID: 32863214 DOI: 10.1016/j.redox.2020.101635]

54 **Yang Y**, Li X, Liu Z, Ruan X, Wang H, Zhang Q, Cao L, Song L, Chen Y, Sun Y. Moderate Treadmill Exercise Alleviates NAFLD by Regulating the Biogenesis and Autophagy of Lipid Droplet. *Nutrients* 2022; **14** [PMID: 36432597 DOI: 10.3390/nu14224910]

55 **Fukuo Y**, Yamashina S, Sonoue H, Arakawa A, Nakadera E, Aoyama T, Uchiyama A, Kon K, Ikejima K, Watanabe S. Abnormality of autophagic function and cathepsin expression in the liver from patients with non-alcoholic fatty liver disease. *Hepatol Res* 2014; **44**: 1026-1036 [PMID: 24299564 DOI: 10.1111/hepr.12282]

56 **González-Rodríguez A**, Mayoral R, Agra N, Valdecantos MP, Pardo V, Miquilena-Colina ME, Vargas-Castrillón J, Lo Iacono O, Corazzari M, Fimia GM, Piacentini M, Muntané J, Boscá L, García-Monzón C, Martín-Sanz P, Valverde ÁM. Impaired autophagic flux is associated with increased endoplasmic reticulum stress during the development of NAFLD. *Cell Death Dis* 2014; **5**: e1179 [PMID: 24743734 DOI: 10.1038/cddis.2014.162]

57 **Lin YC**, Chang PF, Lin HF, Liu K, Chang MH, Ni YH. Variants in the autophagy-related gene IRGM confer susceptibility to non-alcoholic fatty liver disease by modulating lipophagy. *J Hepatol* 2016; **65**: 1209-1216 [PMID: 27417217 DOI: 10.1016/j.jhep.2016.06.029]

58 **Baselli GA**, Jamialahmadi O, Pelusi S, Ciociola E, Malvestiti F, Saracino M, Santoro L, Cherubini A, Dongiovanni P, Maggioni M, Bianco C, Tavaglione F, Cespiati A, Mancina RM, D'Ambrosio R, Vaira V, Petta S, Miele L, Vespasiani-Gentilucci U, Federico A, Pihlajamaki J, Bugianesi E, Fracanzani AL, Reeves HL, Soardo G, Prati D, Romeo S, Valenti LV; EPIDEMIC Study Investigators. Rare ATG7 genetic variants predispose patients to severe fatty liver disease. *J Hepatol* 2022; **77**: 596-606 [PMID: 35405176 DOI: 10.1016/j.jhep.2022.03.031]

59 **Ding H**, Ge G, Tseng Y, Ma Y, Zhang J, Liu J. Hepatic autophagy fluctuates during the development of non-alcoholic fatty liver disease. *Ann Hepatol* 2020; **19**: 516-522 [PMID: 32553647 DOI: 10.1016/j.aohep.2020.06.001]

60 **Tan X**, Huang X, Lu Z, Chen L, Hu J, Tian X, Qiu Z. The essential effect of mTORC1-dependent lipophagy in non-alcoholic fatty liver disease. *Front Pharmacol* 2023; **14**: 1124003 [PMID: 36969837 DOI: 10.3389/fphar.2023.1124003]

61 **Li HY**, Peng ZG. Targeting lipophagy as a potential therapeutic strategy for nonalcoholic fatty liver disease. *Biochem Pharmacol* 2022; **197**: 114933 [PMID: 35093393 DOI: 10.1016/j.bcp.2022.114933]

62 **Grefhorst A**, van de Peppel IP, Larsen LE, Jonker JW, Holleboom AG. The Role of Lipophagy in the Development and Treatment of Non-Alcoholic Fatty Liver Disease. *Front Endocrinol (Lausanne)* 2020; **11**: 601627 [PMID: 33597924 DOI: 10.3389/fendo.2020.601627]

63 **Kaushik S**, Cuervo AM. Degradation of lipid droplet-associated proteins by chaperone-mediated autophagy facilitates lipolysis. *Nat Cell Biol* 2015; **17**: 759-770 [PMID: 25961502 DOI: 10.1038/ncb3166]

64 **Goodman JM**. The importance of microlipophagy in liver. *Proc Natl Acad Sci U S A* 2021; **118** [PMID: 33380459 DOI: 10.1073/pnas.2024058118]

65 **Liu K**, Qiu D, Liang X, Huang Y, Wang Y, Jia X, Li K, Zhao J, Du C, Qiu X, Cui J, Xiao Z, Qin Y, Zhang Q. Lipotoxicity-induced STING1 activation stimulates MTORC1 and restricts hepatic lipophagy. *Autophagy* 2022; **18**: 860-876 [PMID: 34382907 DOI: 10.1080/15548627.2021.1961072]

66 **Yoo J**, Jeong IK, Ahn KJ, Chung HY, Hwang YC. Fenofibrate, a PPARα agonist, reduces hepatic fat accumulation through the upregulation of TFEB-mediated lipophagy. *Metabolism* 2021; **120**: 154798 [PMID: 33984335 DOI: 10.1016/j.metabol.2021.154798]

67 **Zhang H**, Lu J, Liu H, Guan L, Xu S, Wang Z, Qiu Y, Liu H, Peng L, Men X. Ajugol enhances TFEB-mediated lysosome biogenesis and lipophagy to alleviate non-alcoholic fatty liver disease. *Pharmacol Res* 2021; **174**: 105964 [PMID: 34732369 DOI: 10.1016/j.phrs.2021.105964]

68 **Sinha RA**, Rajak S, Singh BK, Yen PM. Hepatic Lipid Catabolism via PPARα-Lysosomal Crosstalk. *Int J Mol Sci* 2020; **21** [PMID: 32244266 DOI: 10.3390/ijms21072391]

69 **Zhou J**, Sinha RA, Yen PM. The roles of autophagy and thyroid hormone in the pathogenesis and treatment of NAFLD. *Hepatoma Res* 2021; **7**: 72 [PMID: 34786524 DOI: 10.20517/2394-5079.2021.82]

70 **Minami Y**, Hoshino A, Higuchi Y, Hamaguchi M, Kaneko Y, Kirita Y, Taminishi S, Nishiji T, Taruno A, Fukui M, Arany Z, Matoba S. Liver lipophagy ameliorates nonalcoholic steatohepatitis through extracellular lipid secretion. *Nat Commun* 2023; **14**: 4084 [PMID: 37443159 DOI: 10.1038/s41467-023-39404-6]

71 **Shibata M**, Yoshimura K, Furuya N, Koike M, Ueno T, Komatsu M, Arai H, Tanaka K, Kominami E, Uchiyama Y. The MAP1-LC3 conjugation system is involved in lipid droplet formation. *Biochem Biophys Res Commun* 2009; **382**: 419-423 [PMID: 19285958 DOI: 10.1016/j.bbrc.2009.03.039]

72 **Kim KH**, Jeong YT, Oh H, Kim SH, Cho JM, Kim YN, Kim SS, Kim DH, Hur KY, Kim HK, Ko T, Han J, Kim HL, Kim J, Back SH, Komatsu M, Chen H, Chan DC, Konishi M, Itoh N, Choi CS, Lee MS. Autophagy deficiency leads to protection from obesity and insulin resistance by inducing Fgf21 as a mitokine. *Nat Med* 2013; **19**: 83-92 [PMID: 23202295 DOI: 10.1038/nm.3014]

73 **Filali-Mouncef Y**, Hunter C, Roccio F, Zagkou S, Dupont N, Primard C, Proikas-Cezanne T, Reggiori F. The ménage à trois of autophagy, lipid droplets and liver disease. *Autophagy* 2022; **18**: 50-72 [PMID: 33794741 DOI: 10.1080/15548627.2021.1895658]

74 **Koutsifeli P**, Varma U, Daniels LJ, Annandale M, Li X, Neale JPH, Hayes S, Weeks KL, James S, Delbridge LMD, Mellor KM. Glycogen-autophagy: Molecular machinery and cellular mechanisms of glycophagy. *J Biol Chem* 2022; **298**: 102093 [PMID: 35654138 DOI: 10.1016/j.jbc.2022.102093]

75 **Farah BL**, Yen PM, Koeberl DD. Links between autophagy and disorders of glycogen metabolism - Perspectives on pathogenesis and possible treatments. *Mol Genet Metab* 2020; **129**: 3-12 [PMID: 31787497 DOI: 10.1016/j.ymgme.2019.11.005]

76 **Allende DS**, Gawrieh S, Cummings OW, Belt P, Wilson L, Van Natta M, Behling CA, Carpenter D, Gill RM, Kleiner DE, Yeh MM, Chalasani N, Guy CD; NASH Clinical Research Network. Glycogenosis is common in nonalcoholic fatty liver disease and is independently associated with ballooning, but lower steatosis and lower fibrosis. *Liver Int* 2021; **41**: 996-1011 [PMID: 33354866 DOI: 10.1111/liv.14773]

77 **Wright TLF**, Umaña LA, Ramirez CM. Update on glycogen storage disease: primary hepatic involvement. *Curr Opin Pediatr* 2022; **34**: 496-502 [PMID: 35942643 DOI: 10.1097/MOP.0000000000001158]

78 **Farah BL**, Landau DJ, Sinha RA, Brooks ED, Wu Y, Fung SYS, Tanaka T, Hirayama M, Bay BH, Koeberl DD, Yen PM. Induction of autophagy improves hepatic lipid metabolism in glucose-6-phosphatase deficiency. *J Hepatol* 2016; **64**: 370-379 [PMID: 26462884 DOI: 10.1016/j.jhep.2015.10.008]

79 **Lee Y**, Hirose H, Ohneda M, Johnson JH, McGarry JD, Unger RH. Beta-cell lipotoxicity in the pathogenesis of non-insulin-dependent diabetes mellitus of obese rats: impairment in adipocyte-beta-cell relationships. *Proc Natl Acad Sci U S A* 1994; **91**: 10878-10882 [PMID: 7971976 DOI: 10.1073/pnas.91.23.10878]

80 **Hughey CC**, Puchalska P, Crawford PA. Integrating the contributions of mitochondrial oxidative metabolism to lipotoxicity and inflammation in NAFLD pathogenesis. *Biochim Biophys Acta Mol Cell Biol Lipids* 2022; **1867**: 159209 [PMID: 35934297 DOI: 10.1016/j.bbalip.2022.159209]

81 **Branković M**, Jovanović I, Dukić M, Radonjić T, Oprić S, Klašnja S, Zdravković M. Lipotoxicity as the Leading Cause of Non-Alcoholic Steatohepatitis. *Int J Mol Sci* 2022; **23** [PMID: 35563534 DOI: 10.3390/ijms23095146]

82 **Tanaka S**, Hikita H, Tatsumi T, Sakamori R, Nozaki Y, Sakane S, Shiode Y, Nakabori T, Saito Y, Hiramatsu N, Tabata K, Kawabata T, Hamasaki M, Eguchi H, Nagano H, Yoshimori T, Takehara T. Rubicon inhibits autophagy and accelerates hepatocyte apoptosis and lipid accumulation in nonalcoholic fatty liver disease in mice. *Hepatology* 2016; **64**: 1994-2014 [PMID: 27637015 DOI: 10.1002/hep.28820]

83 **Frietze KK**, Brown AM, Das D, Franks RG, Cunningham JL, Hayward M, Nickels JT Jr. Lipotoxicity reduces DDX58/Rig-1 expression and activity leading to impaired autophagy and cell death. *Autophagy* 2022; **18**: 142-160 [PMID: 33966599 DOI: 10.1080/15548627.2021.1920818]

84 **Sinha RA**. Autophagy: A Cellular Guardian against Hepatic Lipotoxicity. *Genes (Basel)* 2023; **14**: 553 [PMID: 36874473 DOI: 10.3390/genes14030553]

85 **Ma X**, McKeen T, Zhang J, Ding WX. Role and Mechanisms of Mitophagy in Liver Diseases. *Cells* 2020; **9** [PMID: 32244304 DOI: 10.3390/cells9040837]

86 **Undamatla R**, Fagunloye OG, Chen J, Edmunds LR, Murali A, Mills A, Xie B, Pangburn MM, Sipula I, Gibson G, St Croix C, Jurczak MJ. Reduced mitophagy is an early feature of NAFLD and liver-specific PARKIN knockout hastens the onset of steatosis, inflammation and fibrosis. *Sci Rep* 2023; **13**: 7575 [PMID: 37165006 DOI: 10.1038/s41598-023-34710-x]

87 **Moore MP**, Cunningham RP, Meers GM, Johnson SA, Wheeler AA, Ganga RR, Spencer NM, Pitt JB, Diaz-Arias A, Swi AIA, Hammoud GM, Ibdah JA, Parks EJ, Rector RS. Compromised hepatic mitochondrial fatty acid oxidation and reduced markers of mitochondrial turnover in human NAFLD. *Hepatology* 2022; **76**: 1452-1465 [PMID: 35000203 DOI: 10.1002/hep.32324]

88 **Zhang NP**, Liu XJ, Xie L, Shen XZ, Wu J. Impaired mitophagy triggers NLRP3 inflammasome activation during the progression from nonalcoholic fatty liver to nonalcoholic steatohepatitis. *Lab Invest* 2019; **99**: 749-763 [PMID: 30700851 DOI: 10.1038/s41374-018-0177-6]

89 **Yamada T**, Murata D, Adachi Y, Itoh K, Kameoka S, Igarashi A, Kato T, Araki Y, Huganir RL, Dawson TM, Yanagawa T, Okamoto K, Iijima M, Sesaki H. Mitochondrial Stasis Reveals p62-Mediated Ubiquitination in Parkin-Independent Mitophagy and Mitigates Nonalcoholic Fatty Liver Disease. *Cell Metab* 2018; **28**: 588-604.e5 [PMID: 30017357 DOI: 10.1016/j.cmet.2018.06.014]

90 **Sheldon RD**, Meers GM, Morris EM, Linden MA, Cunningham RP, Ibdah JA, Thyfault JP, Laughlin MH, Rector RS. eNOS deletion impairs mitochondrial quality control and exacerbates Western diet-induced NASH. *Am J Physiol Endocrinol Metab* 2019; **317**: E605-E616 [PMID: 31361543 DOI: 10.1152/ajpendo.00096.2019]

91 **Zhou T**, Chang L, Luo Y, Zhou Y, Zhang J. Mst1 inhibition attenuates non-alcoholic fatty liver disease via reversing Parkin-related mitophagy. *Redox Biol* 2019; **21**: 101120 [PMID: 30708325 DOI: 10.1016/j.redox.2019.101120]

92 **Li X**, Shi Z, Zhu Y, Shen T, Wang H, Shui G, Loor JJ, Fang Z, Chen M, Wang X, Peng Z, Song Y, Wang Z, Du X, Liu G. Cyanidin-3-O-glucoside improves non-alcoholic fatty liver disease by promoting PINK1-mediated mitophagy in mice. *Br J Pharmacol* 2020; **177**: 3591-3607 [PMID: 32343398 DOI: 10.1111/bph.15083]

93 **Cai J**, Huang J, Yang J, Chen X, Zhang H, Zhu Y, Liu Q, Zhang Z. The protective effect of selenoprotein M on non-alcoholic fatty liver disease: the role of the AMPKα1-MFN2 pathway and Parkin mitophagy. *Cell Mol Life Sci* 2022; **79**: 354 [PMID: 35678878 DOI: 10.1007/s00018-022-04385-0]

94 **Dong Y**, Yu M, Wu Y, Xia T, Wang L, Song K, Zhang C, Lu K, Rahimnejad S. Hydroxytyrosol Promotes the Mitochondrial Function through Activating Mitophagy. *Antioxidants (Basel)* 2022; **11** [PMID: 35624756 DOI: 10.3390/antiox11050893]

95 **Chen S**, Wang X, Liu Z, Wang J, Guo Y, Wang Q, Huang H, Li Y, Yu C, Xu C. Olfactomedin 4 deletion exacerbates nonalcoholic fatty liver disease through P62-dependent mitophagy in mice. *Metabolism* 2023; **148**: 155679 [PMID: 37611821 DOI: 10.1016/j.metabol.2023.155679]

96 **Jin K**, Shi Y, Zhang H, Zhangyuan G, Wang F, Li S, Chen C, Zhang J, Wang H, Zhang W, Sun B. A TNFα/Miz1-positive feedback loop inhibits mitophagy in hepatocytes and propagates non-alcoholic steatohepatitis. *J Hepatol* 2023; **79**: 403-416 [PMID: 37040844 DOI: 10.1016/j.jhep.2023.03.039]

97 **Wang L**, Liu X, Nie J, Zhang J, Kimball SR, Zhang H, Zhang WJ, Jefferson LS, Cheng Z, Ji Q, Shi Y. ALCAT1 controls mitochondrial etiology of fatty liver diseases, linking defective mitophagy to steatosis. *Hepatology* 2015; **61**: 486-496 [PMID: 25203315 DOI: 10.1002/hep.27420]

98 **Cao P**, Wang Y, Zhang C, Sullivan MA, Chen W, Jing X, Yu H, Li F, Wang Q, Zhou Z, Wang Q, Tian W, Qiu Z, Luo L. Quercetin ameliorates nonalcoholic fatty liver disease (NAFLD) via the promotion of AMPK-mediated hepatic mitophagy. *J Nutr Biochem* 2023; **120**: 109414 [PMID: 37423322 DOI: 10.1016/j.jnutbio.2023.109414]

99 **Li R**, Xin T, Li D, Wang C, Zhu H, Zhou H. Therapeutic effect of Sirtuin 3 on ameliorating nonalcoholic fatty liver disease: The role of the ERK-CREB pathway and Bnip3-mediated mitophagy. *Redox Biol* 2018; **18**: 229-243 [PMID: 30056271 DOI: 10.1016/j.redox.2018.07.011]

100 **Sinha RA**, Yen PM. Thyroid hormone-mediated autophagy and mitochondrial turnover in NAFLD. *Cell Biosci* 2016; **6**: 46 [PMID: 27437098 DOI: 10.1186/s13578-016-0113-7]

101 **Lee DH**, Park JS, Lee YS, Han J, Lee DK, Kwon SW, Han DH, Lee YH, Bae SH. SQSTM1/p62 activates NFE2L2/NRF2 via ULK1-mediated autophagic KEAP1 degradation and protects mouse liver from lipotoxicity. *Autophagy* 2020; **16**: 1949-1973 [PMID: 31913745 DOI: 10.1080/15548627.2020.1712108]

102 **Park JS**, Lee DH, Lee YS, Oh E, Bae KH, Oh KJ, Kim H, Bae SH. Dual roles of ULK1 (unc-51 like autophagy activating kinase 1) in cytoprotection against lipotoxicity. *Autophagy* 2020; **16**: 86-105 [PMID: 30907226 DOI: 10.1080/15548627.2019.1598751]

103 **Lake AD**, Novak P, Hardwick RN, Flores-Keown B, Zhao F, Klimecki WT, Cherrington NJ. The adaptive endoplasmic reticulum stress response to lipotoxicity in progressive human nonalcoholic fatty liver disease. *Toxicol Sci* 2014; **137**: 26-35 [PMID: 24097666 DOI: 10.1093/toxsci/kft230]

104 **Ariyama H**, Kono N, Matsuda S, Inoue T, Arai H. Decrease in membrane phospholipid unsaturation induces unfolded protein response. *J Biol Chem* 2010; **285**: 22027-22035 [PMID: 20489212 DOI: 10.1074/jbc.M110.126870]

105 **Leamy AK**, Egnatchik RA, Shiota M, Ivanova PT, Myers DS, Brown HA, Young JD. Enhanced synthesis of saturated phospholipids is associated with ER stress and lipotoxicity in palmitate treated hepatic cells. *J Lipid Res* 2014; **55**: 1478-1488 [PMID: 24859739 DOI: 10.1194/jlr.M050237]

106 **Cazanave SC**, Elmi NA, Akazawa Y, Bronk SF, Mott JL, Gores GJ. CHOP and AP-1 cooperatively mediate PUMA expression during lipoapoptosis. *Am J Physiol Gastrointest Liver Physiol* 2010; **299**: G236-G243 [PMID: 20430872 DOI: 10.1152/ajpgi.00091.2010]

107 **Duwaerts CC**, Maiers JL. ER Disposal Pathways in Chronic Liver Disease: Protective, Pathogenic, and Potential Therapeutic Targets. *Front Mol Biosci* 2021; **8**: 804097 [PMID: 35174209 DOI: 10.3389/fmolb.2021.804097]

108 **Yang L**, Li P, Fu S, Calay ES, Hotamisligil GS. Defective hepatic autophagy in obesity promotes ER stress and causes insulin resistance. *Cell Metab* 2010; **11**: 467-478 [PMID: 20519119 DOI: 10.1016/j.cmet.2010.04.005]

109 **Beier JI**, Banales JM. Pyroptosis: An inflammatory link between NAFLD and NASH with potential therapeutic implications. *J Hepatol* 2018; **68**: 643-645 [PMID: 29408544 DOI: 10.1016/j.jhep.2018.01.017]

110 **Koh EH**, Yoon JE, Ko MS, Leem J, Yun JY, Hong CH, Cho YK, Lee SE, Jang JE, Baek JY, Yoo HJ, Kim SJ, Sung CO, Lim JS, Jeong WI, Back SH, Baek IJ, Torres S, Solsona-Vilarrasa E, Conde de la Rosa L, Garcia-Ruiz C, Feldstein AE, Fernandez-Checa JC, Lee KU. Sphingomyelin synthase 1 mediates hepatocyte pyroptosis to trigger non-alcoholic steatohepatitis. *Gut* 2021; **70**: 1954-1964 [PMID: 33208407 DOI: 10.1136/gutjnl-2020-322509]

111 **Xu L**, Zhou J, Che J, Wang H, Yang W, Zhou W, Zhao H. Mitochondrial DNA enables AIM2 inflammasome activation and hepatocyte pyroptosis in nonalcoholic fatty liver disease. *Am J Physiol Gastrointest Liver Physiol* 2021; **320**: G1034-G1044 [PMID: 33728991 DOI: 10.1152/ajpgi.00431.2020]

112 **Yu L**, Hong W, Lu S, Li Y, Guan Y, Weng X, Feng Z. The NLRP3 Inflammasome in Non-Alcoholic Fatty Liver Disease and Steatohepatitis: Therapeutic Targets and Treatment. *Front Pharmacol* 2022; **13**: 780496 [PMID: 35350750 DOI: 10.3389/fphar.2022.780496]

113 **Yamada A**, Hikichi M, Nozawa T, Nakagawa I. FBXO2/SCF ubiquitin ligase complex directs xenophagy through recognizing bacterial surface glycan. *EMBO Rep* 2021; **22**: e52584 [PMID: 34515398 DOI: 10.15252/embr.202152584]

114 **Shapouri-Moghaddam A**, Mohammadian S, Vazini H, Taghadosi M, Esmaeili SA, Mardani F, Seifi B, Mohammadi A, Afshari JT, Sahebkar A. Macrophage plasticity, polarization, and function in health and disease. *J Cell Physiol* 2018; **233**: 6425-6440 [PMID: 29319160 DOI: 10.1002/jcp.26429]

115 **Xu J**, Zhang J, Zhang Z, Gao Z, Qi Y, Qiu W, Pan Z, Guo Q, Li B, Zhao S, Guo X, Qian M, Chen Z, Wang S, Gao X, Zhang S, Wang H, Guo X, Zhang P, Zhao R, Xue H, Li G. Hypoxic glioma-derived exosomes promote M2-like macrophage polarization by enhancing autophagy induction. *Cell Death Dis* 2021; **12**: 373 [PMID: 33828078 DOI: 10.1038/s41419-021-03664-1]

116 **Liu T**, Wang L, Liang P, Wang X, Liu Y, Cai J, She Y, Wang D, Wang Z, Guo Z, Bates S, Xia X, Huang J, Cui J. USP19 suppresses inflammation and promotes M2-like macrophage polarization by manipulating NLRP3 function via autophagy. *Cell Mol Immunol* 2021; **18**: 2431-2442 [PMID: 33097834 DOI: 10.1038/s41423-020-00567-7]

117 **Wen JH**, Li DY, Liang S, Yang C, Tang JX, Liu HF. Macrophage autophagy in macrophage polarization, chronic inflammation and organ fibrosis. *Front Immunol* 2022; **13**: 946832 [PMID: 36275654 DOI: 10.3389/fimmu.2022.946832]

118 **Wynn TA**, Barron L. Macrophages: master regulators of inflammation and fibrosis. *Semin Liver Dis* 2010; **30**: 245-257 [PMID: 20665377 DOI: 10.1055/s-0030-1255354]

119 **Mack M**. Inflammation and fibrosis. *Matrix Biol* 2018; **68-69**: 106-121 [PMID: 29196207 DOI: 10.1016/j.matbio.2017.11.010]

120 **Wang C**, Ma C, Gong L, Guo Y, Fu K, Zhang Y, Zhou H, Li Y. Macrophage Polarization and Its Role in Liver Disease. *Front Immunol* 2021; **12**: 803037 [PMID: 34970275 DOI: 10.3389/fimmu.2021.803037]

121 **Lodder J**, Denaës T, Chobert MN, Wan J, El-Benna J, Pawlotsky JM, Lotersztajn S, Teixeira-Clerc F. Macrophage autophagy protects against liver fibrosis in mice. *Autophagy* 2015; **11**: 1280-1292 [PMID: 26061908 DOI: 10.1080/15548627.2015.1058473]

122 **Sun K**, Xu L, Jing Y, Han Z, Chen X, Cai C, Zhao P, Zhao X, Yang L, Wei L. Autophagy-deficient Kupffer cells promote tumorigenesis by enhancing mtROS-NF-κB-IL1α/β-dependent inflammation and fibrosis during the preneoplastic stage of hepatocarcinogenesis. *Cancer Lett* 2017; **388**: 198-207 [PMID: 28011320 DOI: 10.1016/j.canlet.2016.12.004]

123 **Ilyas G**, Zhao E, Liu K, Lin Y, Tesfa L, Tanaka KE, Czaja MJ. Macrophage autophagy limits acute toxic liver injury in mice through down regulation of interleukin-1β. *J Hepatol* 2016; **64**: 118-127 [PMID: 26325539 DOI: 10.1016/j.jhep.2015.08.019]

124 **Zhou S**, Gu J, Liu R, Wei S, Wang Q, Shen H, Dai Y, Zhou H, Zhang F, Lu L. Spermine Alleviates Acute Liver Injury by Inhibiting Liver-Resident Macrophage Pro-Inflammatory Response Through ATG5-Dependent Autophagy. *Front Immunol* 2018; **9**: 948 [PMID: 29770139 DOI: 10.3389/fimmu.2018.00948]

125 **Wan J**, Weiss E, Ben Mkaddem S, Mabire M, Choinier PM, Picq O, Thibault-Sogorb T, Hegde P, Pishvaie D, Bens M, Broer L, Gilgenkrantz H, Moreau R, Saveanu L, Codogno P, Monteiro RC, Lotersztajn S. LC3-associated phagocytosis protects against inflammation and liver fibrosis via immunoreceptor inhibitory signaling. *Sci Transl Med* 2020; **12** [PMID: 32295902 DOI: 10.1126/scitranslmed.aaw8523]

126 **Ceni E**, Mello T, Galli A. Pathogenesis of alcoholic liver disease: role of oxidative metabolism. *World J Gastroenterol* 2014; **20**: 17756-17772 [PMID: 25548474 DOI: 10.3748/wjg.v20.i47.17756]

127 **Tsuchida T**, Friedman SL. Mechanisms of hepatic stellate cell activation. *Nat Rev Gastroenterol Hepatol* 2017; **14**: 397-411 [PMID: 28487545 DOI: 10.1038/nrgastro.2017.38]

128 **Thoen LF**, Guimarães EL, Dollé L, Mannaerts I, Najimi M, Sokal E, van Grunsven LA. A role for autophagy during hepatic stellate cell activation. *J Hepatol* 2011; **55**: 1353-1360 [PMID: 21803012 DOI: 10.1016/j.jhep.2011.07.010]

129 **Qiu S**, Xu H, Lin Z, Liu F, Tan F. The blockade of lipophagy pathway is necessary for docosahexaenoic acid to regulate lipid droplet turnover in hepatic stellate cells. *Biomed Pharmacother* 2019; **109**: 1841-1850 [PMID: 30551439 DOI: 10.1016/j.biopha.2018.11.035]

130 **Zhang XW**, Zhou JC, Peng D, Hua F, Li K, Yu JJ, Lv XX, Cui B, Liu SS, Yu JM, Wang F, Jin CC, Yang ZN, Zhao CX, Hou XY, Huang B, Hu ZW. Disrupting the TRIB3-SQSTM1 interaction reduces liver fibrosis by restoring autophagy and suppressing exosome-mediated HSC activation. *Autophagy* 2020; **16**: 782-796 [PMID: 31286822 DOI: 10.1080/15548627.2019.1635383]

131 **Gao J**, Wei B, de Assuncao TM, Liu Z, Hu X, Ibrahim S, Cooper SA, Cao S, Shah VH, Kostallari E. Hepatic stellate cell autophagy inhibits extracellular vesicle release to attenuate liver fibrosis. *J Hepatol* 2020; **73**: 1144-1154 [PMID: 32389810 DOI: 10.1016/j.jhep.2020.04.044]

132 **Yu X**, Elfimova N, Müller M, Bachurski D, Koitzsch U, Drebber U, Mahabir E, Hansen HP, Friedman SL, Klein S, Dienes HP, Hösel M, Buettner R, Trebicka J, Kondylis V, Mannaerts I, Odenthal M. Autophagy-Related Activation of Hepatic Stellate Cells Reduces Cellular miR-29a by Promoting Its Vesicular Secretion. *Cell Mol Gastroenterol Hepatol* 2022; **13**: 1701-1716 [PMID: 35219894 DOI: 10.1016/j.jcmgh.2022.02.013]

133 **Ruart M**, Chavarria L, Campreciós G, Suárez-Herrera N, Montironi C, Guixé-Muntet S, Bosch J, Friedman SL, Garcia-Pagán JC, Hernández-Gea V. Impaired endothelial autophagy promotes liver fibrosis by aggravating the oxidative stress response during acute liver injury. *J Hepatol* 2019; **70**: 458-469 [PMID: 30367898 DOI: 10.1016/j.jhep.2018.10.015]

134 **Allaire M**, Rautou PE, Codogno P, Lotersztajn S. Autophagy in liver diseases: Time for translation? *J Hepatol* 2019; **70**: 985-998 [PMID: 30711404 DOI: 10.1016/j.jhep.2019.01.026]

135 **Hammoutene A**, Biquard L, Lasselin J, Kheloufi M, Tanguy M, Vion AC, Mérian J, Colnot N, Loyer X, Tedgui A, Codogno P, Lotersztajn S, Paradis V, Boulanger CM, Rautou PE. A defect in endothelial autophagy occurs in patients with non-alcoholic steatohepatitis and promotes inflammation and fibrosis. *J Hepatol* 2020; **72**: 528-538 [PMID: 31726115 DOI: 10.1016/j.jhep.2019.10.028]

**Footnotes**

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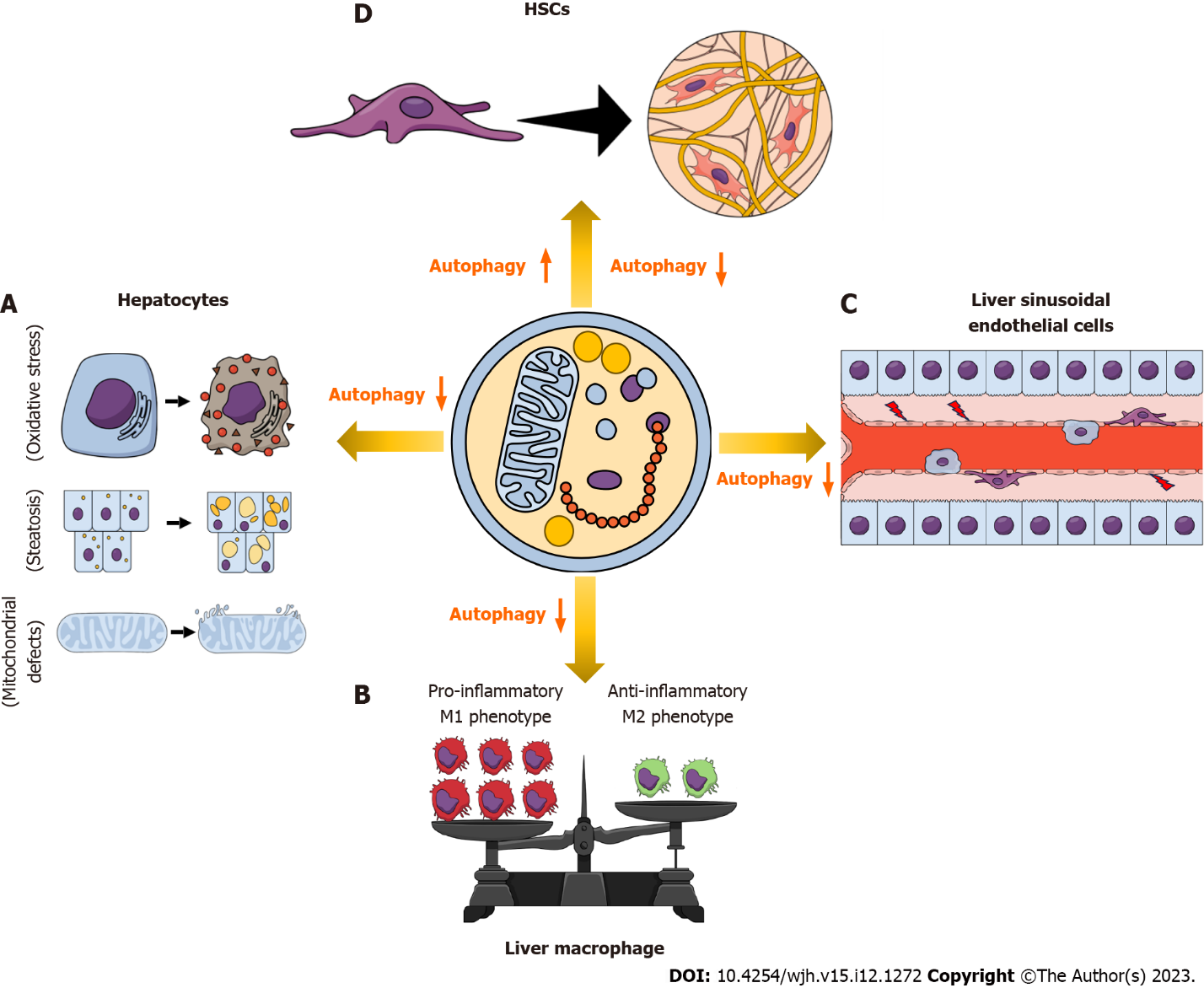
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**Figure Legends**



**Figure 1 Cell-specific effects of autophagy modulation on liver pathology in non-alcoholic fatty liver disease.** A: Hepatocytes: Loss of autophagy results in accumulation of oxidative protein and lipid adducts, triacylglycerols and defective mitochondria; B: Macrophage/Kupffer cells: Inhibition of macrophage autophagy results in increased generation of pro-inflammatory M1 polarized macrophages, which increases inflammation during non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis progression; C: Liver sinusoidal endothelial cells (LSECs): Loss of autophagy in LSECs results in cellular stress and loss of cellular integrity, resulting in increased NAFLD progression; D: Hepatic stellate cells (HSCs): The effect of autophagy on HSCs is conflicting, with some studies demonstrating its anti-fibrotic action while others support its pro-fibrotic action by regulating the transformation of quiescent HSCs into collagen-secreting myofibroblasts. HSCs: Hepatic stellate cells.



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