

World Journal of *Hepatology*

World J Hepatol 2023 December 27; 15(12): 1253-1343



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INDEXING/ABSTRACTING

The *WJH* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (ESCI), Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJH* as 2.4.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yi-Xuan Cai, 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

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PUBLICATION DATE

December 27, 2023

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PUBLISHING PARTNER

Department of Infectious Diseases, the Second Affiliated Hospital of Xi'an Jiaotong University

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>

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

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

POLICY OF CO-AUTHORS

<WebSite><https://www.wjnet.com/bpg/GerInfo/310/</WebSite>>

ARTICLE PROCESSING CHARGE

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

STEPS FOR SUBMITTING MANUSCRIPTS

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

ONLINE SUBMISSION

<https://www.f6publishing.com>

PUBLISHING PARTNER'S OFFICIAL WEBSITE

http://2yuan.xjtu.edu.cn/Html/Departments/Main/Index_21148.html



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

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Cao ZF, China; He X, China

Received: September 25, 2023

Peer-review started: September 25, 2023

First decision: November 3, 2023

Revised: November 7, 2023

Accepted: December 8, 2023

Article in press: December 8, 2023

Published online: December 27, 2023



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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.

Citation: Raza S, Rajak S, Singh R, Zhou J, Sinha RA, Goel A. Cell-type specific role of autophagy in the liver and its implications in non-alcoholic fatty liver disease. *World J Hepatol* 2023; 15(12): 1272-1283

URL: <https://www.wjgnet.com/1948-5182/full/v15/i12/1272.htm>

DOI: <https://dx.doi.org/10.4254/wjh.v15.i12.1272>

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].

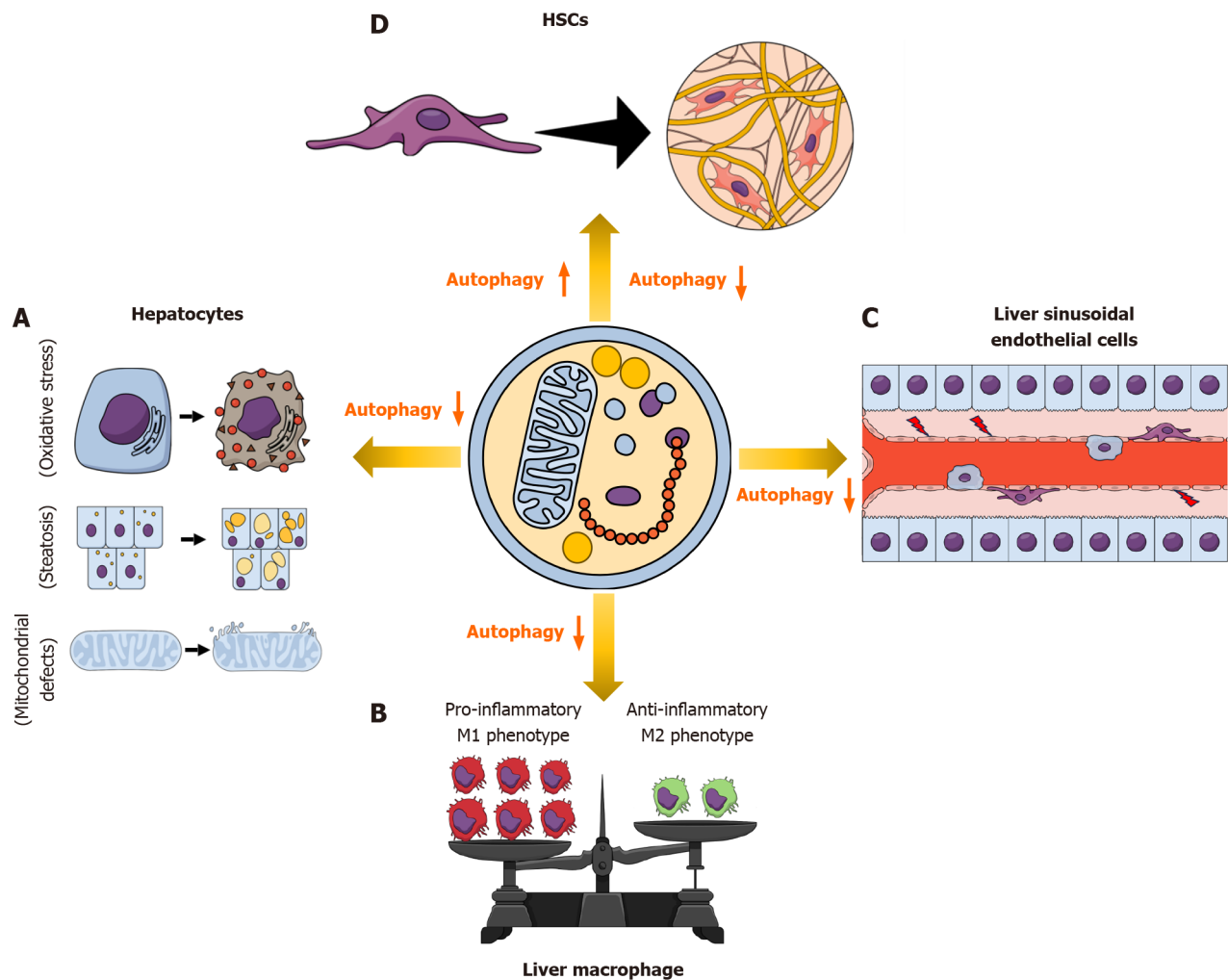
Besides its role in lipid metabolism, autophagy also plays a significant role in hepatocyte carbohydrate metabolism by regulating glycogen breakdown[74]. The lysosomal α -acid glucosidase can hydrolyze glycogen and release free glucose [75]. Excessive glycogen deposition in hepatocytes commonly coexists 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].



DOI: 10.4254/wjh.v15.i12.1272 Copyright ©The Author(s) 2023.

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.

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-1 α , 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-inflammasome signaling, leading to the activation of interleukin (IL)-1 β 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- κ B/IL-1 α / β pathway in autophagy-deficient liver macrophages[122]. Macrophage autophagy was reported to downregulate hepatic inflammation by inhibiting inflammasome-dependent IL-1 β 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.

FOOTNOTES

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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.

Supported by Wellcome Trust/DBT India Alliance Fellowship, No. IA/I/16/2/502691; SERB, No. CRG/2022/002149; Young Scientist Grant, No. YSS/2020/000009/PRCYSS.

Conflict-of-interest statement: The authors declare no conflict of interest.

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S-Editor: Qu XL

L-Editor: Webster JR

P-Editor: Yuan YY

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