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Autophagy in liver diseases: A matter of what to remove and whether to keep

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1. Introduction

There are three types of autophagy, macroautophagy, microautophagy and chaperon-mediated autophagy. Macroautophagy is the largest in terms of the scale, and often briefly referred to as autophagy as here. In recent years, researches in the field of autophagy have become such a strong trend that many new findings have been made that advance not only the understanding of the biology of autophagy, but also the understanding of diseases in various organ systems. This is no exception for the liver, in which autophagy is known to be important for the cellular homeostasis, for the metabolism regulation, and for the pathogenesis of liver diseases ranging from simple steatosis to advanced hepatocellular carcinoma (HCC). This issue of *Liver Research* is dedicated to the recent advances in the understanding of the function and role of autophagy in liver diseases. The editors are hoping that organizing such an issue contributed by leading experts in the field will promote the study of autophagy in the liver and in turn find better ways to treat liver-related illness.

Notably, observations of autophagy in the hepatocyte were among the earliest studies of this fundamental, evolutionarily conserved phenomenon.^{1,2} The liver has been an essential mammalian system for the study of autophagy. In the pre-yeast days, many of the important findings regarding autophagy, such as the morphology of autophagosomes, the relationship with protein degradation, the important role of autophagy in metabolism, were made in the liver system.^{2,3} With the introduction of yeast genetics in the early 1990s, autophagy research entered the molecular times.⁴ At present more than 40 genes in the core autophagy pathways, known as the *autophagy-related* (Atg) genes, have been reported, many of which are evolutionarily conserved.⁴ The discovery of these genes has provided the molecular maps for the mechanisms by which autophagy is activated and executed. In addition, they are critical tools to study the role of autophagy in the pathogenesis of many diseases.

The articles by Khambu *et al.*,⁵ Hikita *et al.*,⁶ and Ma *et al.*⁷ reviewed the concept and the basic machinery of autophagy with an emphasis on different steps. In addition, the major signaling pathways of mammalian target of rapamycin (mTOR) and AMP-activated protein

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Conflict of interest

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kinase (AMPK) are discussed for their roles in regulating autophagy activation. These pathways are often disturbed in the disease context, such as in the fatty liver disease (FLD) and stress conditions, thus can be part of the molecular changes along with autophagy dysfunction, contributing to the pathogenesis.

Our understanding of autophagy has also become more accurate and defined at the subcellular level. The autophagy process is better categorized as the selective and non-selective ones. In the early days, autophagy is considered to be non-selective, engulfing all types of cytosolic components randomly. We now know that this may not be the case under a majority of conditions. Instead, selective removal of a specific type of organelle may be a more routine process than previously thought. Thus specific terminologies for removing a particular type of organelle have evolved, such as lipophagy for removing lipid droplets, mitophagy for removing mitochondria and endoplasmic reticulum (ER)-phagy for removing ER. Specific adaptor molecules are involved in the recognition of the targets by the autophagosomes (see the review by Khambu *et al.*⁵ and Ma *et al.*⁷).

2. Lipophagy and FLD

The review by Khambu *et al.*⁵ summarized the role of autophagy in FLD. FLD is now the most common liver disease, which can be caused by alcohols (alcoholic fatty liver disease (AFLD)), or other non-alcoholic factors (non-alcoholic fatty liver disease (NAFLD)), among which the most common one is the uptake of superfluous nutrients. The early and common presentation of FLD is the benign hepatic steatosis, which can progress to steatohepatitis in a sub-population of patients. Autophagy may play an important role in the early stage of FLD by removing lipid droplets, a process known as lipophagy. In alcoholic liver disease, autophagy may also be important in removing damaged mitochondria via mitophagy, thus reducing cellular injury.

Autophagy can be upregulated by acute alcohol treatment,⁸ but can be suppressed in chronic alcoholic condition.^{9,10} Autophagy can be rapidly suppressed in mice fed with a high fat diet.¹¹ Both the reviews by Khambu *et al.*⁵ and Hikita *et al.*⁶ have summarized these findings in different aspects. Notably, autophagy dysfunction may promote apoptosis, a key step in the progression of benign steatosis to steatohepatitis. Promoting autophagy pharmacologically can improve, whereas inhibition of autophagy can exacerbate, the liver injury.⁹

There are several potential mechanisms that may explain the suppression of autophagy in NAFLD. One is at the initiation stage, in which the activation of mTOR can suppress autophagy activation via the phosphorylation of unc-51 like autophagy activating kinase 1 (ULK1), and suppress autophagy degradation via the phosphorylation of transcription factor EB (TFEB).¹² TFEB is a master control gene for lysosome biogenesis and lysosomal function, which paradoxically supports mTOR activation.¹³ This mTOR-TFEB regulatory loop can dynamically impact the disease progression in NAFLD.¹¹ These signaling components are reviewed in the article by Khambu *et al.*⁵

The other key point where autophagy may be arrested in FLD is the step of the fusion of the autophagosome with the lysosome. This was briefly discussed in Khambu *et al.*⁵ but is extensively discussed in the review by Hikita *et al.*⁶ Here, the article summarized the recent understanding of the molecular components involved in the autophagosome-lysosome fusion. Furthermore the authors tried to examine the potential involvement of the molecular changes in liver diseases, with a particular emphasis on a molecule known as Rubicon. Rubicon is a part of beclin-1 complex and is known to be inhibitory on autophagy. Rubicon can thus suppress the autophagosome-lysosome fusion. The role of Rubicon in NAFLD-induced liver injury was a key discovery from the authors' laboratory, which suggests that it may be suitable for future interventions to rescue autophagy activity in NAFLD.

3. Mitophagy, aging and ethanol- or ischemia/reperfusion (I/R)-induced injury

As indicated above mitophagy could be important in controlling mitochondrial damage in the alcoholic liver diseases. In fact, mitophagy could occur in many contexts. John Lemasters is a leading expert in mitophagy biology, who first coined the mitophagy term.¹⁴ The review by him and his colleague has defined the mitophagy in three categories, each with distinct molecular mechanisms, structure features and biochemical alterations.¹⁵ The pathophysiological relevance of mitophagy is particularly discussed in the context of ethanol-induced liver toxicity, in which ethanol causes mitochondrial depolarization and type 2 mitophagy. Type 2 mitophagy depends on PTEN-induced kinase 1 (PINK1)/Parkin. It may play roles in reducing ethanol-induced cellular injury. But it may also be important for supporting chronic hepatitis viral infection (see below and Khan *et al.*,¹⁶ 2018).

Mitophagy in I/R injury is also critically important for the recovery of hepatocytes after the injury. The review by Lee and Kim¹⁷ discussed the importance of SIRT1-MFN2 pathway in this process. The key element is the influence of aging and the corresponding role of autophagy in the process. The authors noted the age-related difference in the autophagy pathway and therefore the ability of mitochondrial quality control and hepatocyte survival after I/R injury. This review covered several topics that cross different areas of autophagy, aging, mitochondrial biology and I/R-injury.

4. ER-phagy and ER biology in lipid metabolism and viral infection

Another great example of selective autophagy, perhaps more seen in the hepatocytes than in other cells, is ER-phagy, or selective removal of ER by autophagy. The review by Ma *et al.*⁷ has timely summarized the recent progresses in this area.

ER is a complicated system, participating in many cellular functions related to protein synthesis, lipids and steroid metabolism, calcium regulation and drug metabolism. ER is also a favorite site targeted by virus, such as the hepatitis virus. When ER function is disturbed, ER stress arises, which can trigger multiple pathways, known as unfolded protein response (UPR). UPR can also activate autophagy.¹⁸

ER itself could be subjected to autophagic removal. One of the key functions of ER in the hepatocyte is related to drug metabolism as the cytochrome p450 system is mostly located in the smooth ER. Drug administration can stimulate the expression of cytochrome p450 enzymes and the proliferation of ER. The ER network shrinks after drug withdrawal and much of the ER structure could be removed by autophagosomes. Ma *et al.*⁷ systemically reviewed ER-phagy in the yeast and in the mammalian cells. They have discussed a number of adaptor molecules, or selective receptors, for ER to be recognized by the autophagosomal membranes, and for their potential involvement in liver diseases.

Elimination of intracellular pathogens by autophagy is known as xenophagy. This, however, is not straightforward. Pathogens often have complex interactions with the cellular machinery, in which they may evade or even hijack the autophagy system. Hepatitis B virus (HBV) and hepatitis C virus (HCV) can both fool the cell to activate and to use autophagy for their benefits during their replications. This allows persistent and chronic viral infection. Khan *et al.*¹⁶ have provided a quite comprehensive review on the role of HBV and HCV in autophagy induction and in turn the role of autophagy in the pathological effects of these viruses in the liver. One way HBV and HCV can induce autophagy is via ER stress and UPR. Other mechanisms, including those involving the mitochondria or the Golgi complex are also discussed. A broad scope of literature have been reviewed and different studies, some of which are controversial, are presented in a nicely arranged fashion to help the readers to understand the issues and the mechanisms involved.

5. Autophagy, cell death and hepatic cancer development

In normal cells, autophagy may act as a tumor suppressor by removing damaging organelles, such as mitochondria, and reducing oxidative stress, which can induce tumorigenic mutations.¹⁹ Autophagy may also inhibit hepatic tumor development by inhibiting the release of a damage-associated molecular pattern (DAMP) molecule, high-mobility group box 1 (HMGB1), which promotes tumor growth.²⁰ However, in tumor cells, which are often under various types of stress, some of which are caused by interventional therapy, autophagy can serve as a survival strategy to protect tumor cells.²¹ Interestingly, a recent study has shown that autophagy can be important for the development of hepatic cancer stem cells by preventing mitochondrial p53 from inhibiting the transcription of a stemness factor, NANOG.²² Finally, cell death depending on the autophagy machinery has been reported and known as autophagic death.²³ Thus the role of autophagy in hepatic cancer development could be multiple, depending on the stage of tumorigenesis, and depending on the internal and external driving forces. In the article by Pang and Liu,²⁴ they discussed autophagic cell death in the context of HCC. They discussed several possible mechanisms, by which autophagy is linked to cell death. In particular, the authors proposed that damage-regulated autophagy modulator (DRAM)-mediated mitophagy is linked to a new type of autophagic cell death. A potential significance of this type of cell death is that they may be construed as a new way to treat HCC, e.g., by certain herbal medicines.

Overall, reading through these reviews, one may find that removal of certain subcellular materials, such as lipid droplets, damaged mitochondria or expanded ER, is important to keep hepatocytes healthy and to reduce damages in the case of FLD or I/R injury, or to

reduce tumorigenesis. In this case one may want to maintain and even stimulate the autophagy function. On the other hand, autophagy function can be taken over by cells or virus for their advantage to maintain survival and to proliferate. When survival autophagy occurs in the tumor cells or virus-infected cells one may not want to keep autophagy function. Autophagy can thus be a double-edged sword. Manipulations of autophagy for therapeutic purposes have to consider all these factors and have to be context-dependent in order to be effective.

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