World Journal of Hepatology

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DOI: 10.4254/wjh.v7.i9.1154

World J Hepatol 2015 May 28; 7(9): 1154-1156
ISSN 1948-5182 (online)

EDITORIAL

Ethanol-induced hepatic autophagy: Friend or foe?

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Author contributions: Eid N wrote the paper; Ito Y and Otsuki Y reviewed it.
Conflict-of-interest: The authors declare that they have no conflict of interest.

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Received: January 19, 2015
Peer-review started: January 20, 2015
First decision: February 7, 2015
Revised: February 14, 2015
Accepted: March 30, 2015
Article in press: April 2, 2015
Published online: May 28, 2015

Abstract

Excessive alcohol intake may induce hepatic apoptosis, steatosis, fibrosis, cirrhosis and even cancer. Ethanol-induced activation of general or selective autophagy as mitophagy or lipophagy in hepatocytes is generally considered a prosurvival mechanism. On the other side of the coin, upregulation of autophagy in non-hepatocytes as stellate cells may stimulate fibrogenesis and subsequently induce detrimental effects on the liver. The autophagic response of other non-hepatocytes as macrophages and endothelial cells is unknown yet and needs to be investigated as these cells play important roles in ethanol-induced hepatic steatosis and damage. Selective pharmacological stimulation of autophagy in hepatocytes may be of therapeutic importance in alcoholic liver disease.

Key words: Macrophages; Autophagy; Hepatocytes; Lipophagy; Mitophagy; Stellate cells; Alcohol

Core tip: This short editorial discusses the impact of ethanol-induced upregulation of cytoprotective bulk and selective autophagy as mitophagy or lipohagy on various types of liver cells. While ethanol-induced activation of autophagy in hepatocytes is generally prosurvival mechanism, upregulation of autophagy in non-hepatocytes as stellate cells may stimulate fibrogenesis and subsequently induce detrimental effects on the liver as a whole. The autophagic response of other non-hepatocytes as macrophages and endothelial cells is unknown yet and needs to be investigated as these cells play important roles in ethanol-induced hepatic steatosis and damage.

Eid N, Ito Y, Otsuki Y. Ethanol-induced hepatic autophagy: Friend or foe? *World J Hepatol* 2015; 7(9): 1154-1156 Available from: URL: http://www.wjgnet.com/1948-5182/full/v7/i9/1154.htm DOI: http://dx.doi.org/10.4254/wjh.v7.i9.1154

TEXT

Excessive alcohol intake may induce hepatic apoptosis, steatosis, fibrosis, cirrhosis and even cancer. Although ethanol-induced autophagy in hepatocytes has been recently considered as antiapoptotic mechanism, activation of autophagy in non-hepatocytes as macrophages, endothelial cells and stellate cells is not clearly known yet. More importantly, whether ethanol-induced activation of autophagy in non-hepatocytes is protective or detrimental to the liver as a whole needs to be

explored.

Autophagy is a cytoprotective pathway for clearance of damaged proapoptotic cellular components following multiple forms of stress, including oxidative stress, endoplasmic reticulum stress, mitochondrial damage and excessive accumulation of lipid droplets (LDs). Morphologically, autophagy is characterized by the formation of isolation membranes, which engulf a region of the cell cytoplasm or selectively an organelle forming autophagosomes mediated by microtubule-associated protein light chain 3 (LC3). The autophagosomes then fuse with lysosomes *via* lysosomal-associated membrane protein 2 (LAMP-2), forming autolysosomes, where the contents of the cargo are digested by lysosomal cathepsins[1-4]. Chronic alcohol consumption may induce hepatic damage, ranging from early-stage steatosis to steatohepatitis, fibrosis, cirrhosis, and ultimately hepatic carcinoma.

Ethanol-induced hepatocyte steatosis is characterized by excessive accumulation of cytoplasmic LDs which may render hepatocytes more susceptible to toxic or stress factors (multi-hit mechanisms) resulting in the progression of alcoholic liver disease. Importantly, ethanol-induced hepatocytes steatosis is often associated with structural and functional mitochondrial damage resulting from ethanol metabolism and related oxidative stress[5,6]. Therefore and as we have reported recently, the selective autophagic clearance of damaged mitochondria (mitophagy) and excessive LDs (lipophagy) in hepatocytes of chronic ethanol-treated rats may be a prosurvival mechanism for prevention of hepatocytes apoptosis (*via* clearance of proapoptotic damaged mitochondria) and progression of hepatic steatosis. We have observed that in addition to the upregulation of general autophagy markers LC3-Ⅱ, LAMP-2 and lysosomal cathepsins in hepatocytes of ethanol-treated rats, there was also overexpression of PINK1 (a sensor of mitochondrial damage and specific marker of mitophagy) in mitochondria of hepatocytes in treated rats[4,6]. Recent studies supported this cytoprotective role of autophagy in response to chronic ethanol toxicity[7,8]. In an interesting study, Lin *et al*[7] observed that there was an enhancement of lipophagy and probably mitophagy in hepatocytes of acute and chronic ethanol-treated mice. Moreover, they found that pharmacological promotion of autophagy by carbamazepine or rapamycin enhanced the autophagic response to ethanol toxicity and subsequently alleviated steatosis and hepatocyte injury, while blocking autophagy elevated steatosis and hepatic injury[7].

On the other hand, a recent study demonstrated that activation of autophagy in hepatic stellate cells of chronic ethanol-treated mice increases hepatic fibrogenesis by providing the fuel necessary to support stellate cell activation; thus accelerating liver pathology[9]. Therefore, it seems that upregulation of autophagy in stellate cells by ethanol may be to some degree detrimental to the liver compared to activation of autophagy in hepatocytes. However, autophagic signaling in stellate cells could be relatively innocuous compared to those in hepatocytes, simply because the hepatocytes make up the bulk of the parenchyma and comprise the main functional element in the liver. Hence, the pro-survival signaling in hepatocytes predominates. Selective pharmacological stimulation of autophagy in hepatocytes may be of therapeutic importance in alcoholic liver disease.

What is unknown yet and needs to be explored: Does ethanol activate autophagy in hepatic macrophages? Is activation of autophagy in Kupffer cells (KCs) by ethanol exposure friend as in case of hepatocytes or foe as in stellate cells? To the best of our knowledge, no studies investigated the autophagic response of KCs to ethanol toxicity although these cells may play important role in hepatic damage under acute and chronic ethanol treatment[10]. An elegant study by Wan *et al*[11] demonstrated that KCs could be either proinflammatory (M1 type) or anti-inflammatory (M2 type) and the balance between the two types impact hepatic damage. They found that in acute and chronic ethanol-treated mice, there was an increase in KCs apoptosis. Further observation revealed that M2 KCs induced apoptosis in M1 counterparts. They suggest that promoting M2-induced M1 KC apoptosis may be cytoprotective for liver under ethanol exposure. Whether autophagy is activated in M2 KCs and switched off in M1 KCs needs to be investigated. Moreover, ethanol-mediated increases in RANTES/CCL5 by liver sinusoidal endothelial cells can promote the infiltration of immunocytes to the liver *via* sinusoids, which may accelerate liver injury. Therefore, there is a possibility of autophagy-mediated upregulation of RANTES/CCL5 in ethanol-exposed liver sinusoidal endothelial cells[12,13].

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P- Reviewer: Heger M, Sirin G, Tsunedomi R, Vespasiani-Gentilucci U
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