**Name of journal: World Journal of Hepatology**

**ESPS Manuscript NO: 16480**

**Columns: Editorial**

**Ethanol-induced hepatic autophagy: Friend or foe?**

Eid N *et al*. Ethanol-induced autophagy in liver

Nabil Eid, Yuko Ito, Yoshinori Otsuki

**Nabil Eid, Yuko Ito, Yoshinori Otsuki,** Department of Anatomy and Cell Biology, Division of Life Sciences, Osaka Medical College, Takatsuki, Osaka 569-8686, Japan

**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.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Correspondence to: Nabil Eid, PhD, MD, Professor**, Department of Anatomy and Cell Biology, Division of Life Sciences, Osaka Medical College, 2-7 Daigaku-machi, Takatsuki, Osaka 569-8686, Japan. nabil@art.osaka-med.ac.jp

**Telephone:** +81-726-831221

**Fax:** +81-726-846511

**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:**

**Published online:**

**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 coin, upregulation of autophagy in non-hepatocytes as stellate cells may stimulate fibrogenesis and subsequently induce detrimental effects on 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:** Alcohol; Autophagy; Hepatocytes; Lipophagy; Macrophages; Mitophagy; Stellate cells

© **The Author(s) 2015**. Published by Baishideng Publishing Group Inc. All rights reserved.

**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 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; In press

**Ethanol-induced hepatic autophagy: Friend or foe?**

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 are not clearly known yet. More importantly, whether ethanol-induced activation of autophagy in non-hepatocytes is protective or detrimental to 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 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 proinflamatory (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].

**REFERENCES**

1 **Kroemer G**, Levine B. Autophagic cell death: the story of a misnomer. *Nat Rev Mol Cell Biol* 2008; **9**: 1004-1010 [PMID: 18971948 DOI: 10.1038/nrm2529]

2 **Kroemer G**, Mariño G, Levine B. Autophagy and the integrated stress response. *Mol Cell* 2010; **40**: 280-293 [PMID: 20965422 DOI: 10.1016/j.molcel.2010.09.023]

3 **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]

4 **Eid N**, Ito Y, Otsuki Y. The autophagic response to alcohol toxicity: the missing layer. *J Hepatol* 2013; **59**: 398 [PMID: 23624249 DOI: 10.1016/j.jhep.2013.03.038]

5 **Feldstein AE**, Bailey SM. Emerging role of redox dysregulation in alcoholic and nonalcoholic fatty liver disease. *Antioxid Redox Signal* 2011; **15**: 421-424 [PMID: 21254858 DOI: 10.1089/ars.2011.3897]

6 **Eid N**, Ito Y, Maemura K, Otsuki Y. Elevated autophagic sequestration of mitochondria and lipid droplets in steatotic hepatocytes of chronic ethanol-treated rats: an immunohistochemical and electron microscopic study. *J Mol Histol* 2013; **44**: 311-326 [PMID: 23371376 DOI: 10.1007/s10735-013-9483-x]

7 **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]

8 **King AL**, Swain TM, Mao Z, Udoh US, Oliva CR, Betancourt AM, Griguer CE, Crowe DR, Lesort M, Bailey SM. Involvement of the mitochondrial permeability transition pore in chronic ethanol-mediated liver injury in mice. *Am J Physiol Gastrointest Liver Physiol* 2014; **306**: G265-G277 [PMID: 24356880 DOI: 10.1152/ajpgi.00278.2013]

9 **Hernández-Gea V**, Ghiassi-Nejad Z, Rozenfeld R, Gordon R, Fiel MI, Yue Z, Czaja MJ, Friedman SL. Autophagy releases lipid that promotes fibrogenesis by activated hepatic stellate cells in mice and in human tissues. *Gastroenterology* 2012; **142**: 938-946 [PMID: 22240484 DOI: 10.1053/j.gastro.2011.12.044]

10 **Cohen JI**, Nagy LE. Pathogenesis of alcoholic liver disease: interactions between parenchymal and non-parenchymal cells. *J Dig Dis* 2011; **12**: 3-9 [PMID: 21091930 DOI: 10.1111/j.1751-2980.2010.00468.x]

11 **Wan J**, Benkdane M, Teixeira-Clerc F, Bonnafous S, Louvet A, Lafdil F, Pecker F, Tran A, Gual P, Mallat A, Lotersztajn S, Pavoine C. M2 Kupffer cells promote M1 Kupffer cell apoptosis: a protective mechanism against alcoholic and nonalcoholic fatty liver disease. *Hepatology* 2014; **59**: 130-142 [PMID: 23832548 DOI: 10.1002/hep.26607]

12 **van Golen RF**, van Gulik TM, Heger M. Mechanistic overview of reactive species-induced degradation of the endothelial glycocalyx during hepatic ischemia/reperfusion injury. *Free Radic Biol Med* 2012; **52**: 1382-1402 [PMID: 22326617 DOI: 10.1016/j.freeradbiomed.2012.01.013]

13 **Yeligar SM**, Machida K, Tsukamoto H, Kalra VK. Ethanol augments RANTES/CCL5 expression in rat liver sinusoidal endothelial cells and human endothelial cells via activation of NF-kappa B, HIF-1 alpha, and AP-1. *J Immunol* 2009; **183**: 5964-5976 [PMID: 19828633 DOI: 10.4049/jimmunol.0901564]

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

**S- Editor:** Gong XM

**L- Editor:** **E- Editor:**