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Autophagy: one of the molecular mechanisms of response to intra-cellular stress in alcohol toxicity

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To the Editor

We appreciate the interest of Eid et al [1] in the Hepatology Snapshot on “Alcohol and toxicity” [2]. The authors posit that autophagy, a physiological mechanism that is ubiquitous and critical for maintaining balance in synthesis, degradation, and recycling of proteins, lipids and other macromolecules, represents the central mechanism that connects key toxicity mediators and molecular mechanisms with alcohol-induced disturbances in target tissues.

Changes in the rate of autophagy are triggered by cell stress and may ultimately result in the autophagic cell death [3]. Abnormal autophagy is now widely implicated in human diseases (e.g., cancer, metabolic and neurodegenerative disorders, cardiovascular and pulmonary ailments) and in aging [4]. Multiple molecular events that are known to regulate autophagy [5], such as misfolded proteins, oxidative stress, disruption of lipid and energy metabolism, are indeed part of alcohol-induced pathophysiology in target tissues.

Recent studies suggest that dysregulated autophagy could play a role in most liver disease such as chronic viral hepatitis B and C, alcoholic and non-alcoholic fatty liver disease and hepatocellular carcinoma [6]. Among them, alcoholic liver disease has been extensively studied, mostly at the experimental level [7]. Alcohol can both induce and suppress autophagy via different molecular pathways including mTOR, phosphatase and tensin homolog (PTEN) and AMP-activated protein kinase (AMPK) [8]. For example, alcohol may suppresses the autophagic process by inhibiting activity of AMPK, resulting in an impaired clearance of Mallory Denk bodies [8, 9]. The complexities of the effects of alcohol on autophagy are probably due to the fact that autophagy is a complex process that may involve non-overlapping triggers, effectors and outcomes [7]. Such contradiction also emerged from studies on the role of autophagy in cancer, where autophagy was shown to be both a tumor-suppression pathway, and a pro-survival mechanism that protects cancer cells [8].

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Based on recent experimental studies [12], it has been recently proposed that promoting autophagy represents a promising therapeutic approach in patients with chronic liver diseases [6]. We think that the current enthusiasm on this strategy should be tempered. First, most data linking liver disease and autophagy derive from experimental models, and translational studies in humans are needed. Second, suppressed autophagy can represent a defensive mechanism of the liver against the metabolic syndrome [10]. And most importantly, prolonged use of drugs interfering with autophagy can lead to severe side effects including impaired liver regeneration and promotion of hepatocellular carcinoma.

In addition, it is less clear what role autophagy may play in alcohol-associated diseases in other tissues and organs. As detailed in Rusyn and Bataller [2], in addition to liver disease, excessive alcohol intake has been linked to pancreatitis, cardiovascular, kidney and neurological diseases, fetal alcohol spectrum disorders, and cancers of the gastrointestinal tract and female breast. Of these additional target tissues, most compelling experimental evidence exists for involvement of autophagy in the development of pancreatitis [11]. It is also apparent that the mechanisms that link autophagy to pancreatitis actually suggest that inhibition of autophagy impairs the development of acute pancreatitis, or more importantly improves its course once the process has started [12]. Very limited experimental evidence exists to determine whether autophagy plays a role in alcohol's adverse effects in the remaining target tissues. Thus, we believe it may be premature to regard autophagy as the central mechanism that connects key toxicity mediators and molecular mechanisms with alcohol-induced histopathological disturbances in tissues other than liver.

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