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

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 diseases 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 suppress the autophagic process by inhibiting the 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].

Based on recent experimental studies [12], it has been 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 the 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 the liver.

Conflict of interest

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References


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Mother-to-infant transmission of hepatitis B virus infection: Significance of maternal viral load and strategies for intervention

To the Editor:

We read with great interest the paper by Wen et al. [1], prospectively evaluating hepatitis B viral load as a significant factor for immunoprophylaxis failure of infants born of hepatitis B surface antigen (HBsAg) positive mothers. The authors suggested that the risk of immunoprophylaxis failure increased with increasing viral load and that intervention, such as anti-viral therapy in mothers with high viral load, may be considered. We agreed with the authors that high maternal viral load correlated with an increased risk of vertical transmission, but the optimal cut-off was yet to be determined [2]. However, we believed that further clarification of the data would be needed before change in clinical practice can be recommended.

First of all, the timing of blood test on the viral load of the subjects was not clearly stated. The authors mentioned that it was checked in the third trimester or within 2 months after delivery. However, the viral load may vary throughout pregnancy and after delivery. In a retrospective study which evaluated the change of viral load in 33 HBsAg positive mothers, of whom 9 were hepatitis B e antigen (HBeAg) positive, it was found that viral load increased by a mean of 0.4 log in late pregnancy or early postpartum, of which four HBeAg negative mothers had >1 log change during pregnancy [3]. In another retrospective study, ter Borg et al. studied 38 HBsAg pregnancies of which 24 were HBeAg positive. Lamivudine was started in the third trimester to reduce the viral load in 13 pregnancies. The median viral load increased from 7.8 log_{10} copies/ml before, to 8.2 log_{10} copies/ml during pregnancy, and then decreased to 6.8 log_{10} copies/ml after delivery [4]. We were not told the reason why a proportion of the women’s blood tests were collected after delivery for viral load testing and not before delivery, in this prospective study. Assuming the postpartum viral load to be similar to the antenatal level may give rise to a wrong conclusion. Therefore, it would be important for the authors to provide the median gestational weeks when the blood test was taken, and to clarify the proportion of mothers having postpartum test. Furthermore, as the authors also pointed out, the result would be more meaningful if the viral load levels were obtained before 28 weeks of gestation. Anti-viral therapy was started from 28 weeks of gestation in most of the trials evaluating the efficacy of anti-viral treatment to decrease the risk of immunoprophylaxis failure in women with high viral load [5]. Viral load quantification in the late third trimester, at delivery, or even after delivery, would be less useful clinically as intervention to alter outcome may not be possible. Caesarean delivery could not decrease the risk of immunoprophylaxis failure [2] and late viral load quantification would not allow adequate time for anti-viral treatment to decrease viral load.

Secondly, we also wondered if any subjects were receiving anti-viral therapy during the studied period. Anti-viral therapy initiated after the blood test before delivery, or vice versa, could affect the viral load level and subsequent correlation with risk of the immunoprophylaxis failure. Thirdly, horizontal transmission of hepatitis B virus was possible [6] in 17.5% of children who were tested for HBsAg at 1–3 years of age. The HBsAg positive status in this group could be due to horizontal infection rather than genuine immunoprophylaxis failure. Finally, we were interested in the high rate of invasive prenatal diagnostic test (amniocentesis/CVS) and first vaccine given beyond 24 hours in the ten infants who suffered from chronic hepatitis B infection. Could these be the potential factors that led to a higher rate of immunoprophylaxis failure? We hope the authors could provide more data on that.

Conflict of interest

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