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EDITORIAL

Jumonji: Welcome to the World of Interferon Signaling in Alcohol and HCV

Alcoholic liver disease and hepatitis C virus (HCV) infection, either alone or in combination, affect 2 out of 3 persons living with chronic liver disease in the Western world. Alcohol consumption not only increases the risk of HCV infection, but also works synergistically with HCV to increase hepatotoxicity and the progression to hepatocellular carcinoma (HCC).[1] It is known that the increase in hepatotoxicity is caused in part by increased viral replication and impaired innate immune responses.[1,2] A novel mechanism for alcohol-accelerated HCV replication is identified in the article by Ganesan et al[3] in this issue of *Cellular and Molecular Gastroenterology and Hepatology*. The critical role of arginine methylation of STAT1 in interferon (IFN)-α-induced JAK-STAT signaling and expression of antiviral genes (ISGs) is well-established. It has previously been shown that this arginine methylation is regulated by protein methyl transferase 1.[4] In a series of elegant experiments, Ganesan et al[3] now demonstrate that demethylation of STAT1 by jumonji-domain containing 6 protein (JMJD6) also disrupts interferon-α signaling and increases HCV replication; and that this process is enhanced by alcohol or an acetaldehyde-generating system (AGS) by upregulation of JMJD6. Notably, HCV (genotype 2a) infection of RLW cells induced a 100% increase in JMJD6, which was further enhanced (50%) by AGS treatment, emphasizing the role of both HCV and alcohol in regulation of JMJD6. This JMJD6 induction corresponded to STAT1 demethylation, suppression of ISGs, and increased replication of HCV. These findings were also corroborated in C57Bl/6 mice (with or without HCV structural proteins), and in chimeric mice with humanized livers. The authors' findings dovetail nicely with a recent article showing that JMJD6 knockdown restores HNF4α levels in alcohol-fed mice. HNF4α regulates hepatocyte proliferation and is downregulated in HCC, and a strong correlation is seen between HNF4α and hepatocyte proliferation in human HCC patient specimens.[5] Together, the findings suggest that inhibition of JMJD6 may also be a promising therapeutic strategy for HCC.

Cotreatment with a promethylating agent, betaine, reversed the effect of AGS on JMJD6 expression in hepatocytes and attenuated JMJD6 expression in RLW cells. These findings were replicated in animal models. The presence of a betaine-homocysteine-S-methyltransferase did not affect JMJD6 expression, indicating that betaine does not regulate AGS-induced JMJD6 expression via this mechanism. Because betaine and the antioxidant *N*-acetylcysteine showed similar effects in attenuating JMJD6 upregulation by AGS, the authors postulate a potential antioxidant role for betaine. This is an exciting avenue for investigation and it will be interesting to determine whether *N*-acetylcysteine attenuation of JMJD6 results in ISG activation and decreased HCV replication as well. If so, there is the potential for *N*-acetylcysteine and/or betaine to be used as adjunct therapy along with direct-acting antivirals to enhance HCV suppression and cure from HCV infection by reducing dose or duration of therapy.

An important question arising from these studies is whether alcohol affects different HCV genotypes differently. The experiments done by Ganesan et al[3] used RLW cells infected with HCV genotype 2a. The knowledge of the extent to which alcohol modulates the replication of different HCV genotypes has implications in clinical practice and may affect the management recommendations of practitioners worldwide. In any case, the authors' findings suggest that hepatologists and clinical practitioners involved in treating HCV patients need to continue to emphasize abstinence from alcohol during the treatment of HCV infection with direct-acting antivirals.

Although this is an exciting time where HCV as a cause of chronic liver disease is on the brink of extinction, there is no doubt that there still is a huge burden of HCV-infected persons in the United States and worldwide that poses a significant demand for liver transplantation because of the development of cirrhosis and HCC. Ganesan et al[3] have opened new vistas for further exploration of the mechanistic role of demethylases, such as JMJD6, and the development of targeted therapies for the clinical management of liver disease associated with alcohol and HCV infection.

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Conflicts of interest
The authors disclose no conflicts.

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