

The Protective Function of PRMT1 in Alcohol-Induced Hepatocellular Carcinoma

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A recent study by Zhao et al.⁽¹⁾ unveiled a previously unappreciated tumor-suppressive activity of protein arginine N-methyltransferase 1 (PRMT1). PRMT1 is a major enzyme for cellular arginine methylation and a potent inhibitor of nitric oxide synthase. PRMT1 has been implicated in the development of several types of tumors, due to its regulation of target proteins involved in either promoting or suppressing cell proliferation. However, its involvement in hepatocellular carcinoma (HCC) development had not been clearly defined. Using a murine model of hepatocyte-specific PRMT1 deletion, Zhao et al. demonstrated that PRMT1 inhibited HCC formation caused by the combined treatment of diethylnitrosamine (DEN) and chronic alcohol feeding

(DEN-alcohol). Interestingly, this tumor-suppressive effect of PRMT1 is specific to the alcohol-related aspects of tumorigenesis. Further mechanistic studies demonstrated that PRMT1 significantly attenuates alcohol-induced oxidative stress, inflammation, and cell death by inhibiting nitric oxide synthase (iNOS).

HCC is responsible for most primary liver cancers. According to the World Health Organization, more than 1 million patients are projected to die from liver cancer by 2030. HCC affects 33,000 people, and 27,000 people die from the disease in the United States, and it is the sixth leading cause of cancer-related death.⁽²⁾ Nearly 90% of the cases of HCC develop in a context of underlying chronic liver disease caused by hepatitis B and C infections, alcohol abuse, or metabolic disorders.⁽³⁾ It is estimated that an alcohol etiology contributes approximately 30% of HCC cases globally. The underlying mechanisms of alcohol-induced HCC are complex and appear to involve genetic and epigenetic risk factors, tissue inflammation, as well as dysregulation of iron, folic acid, and lipid metabolism.⁽⁴⁾ It has been recognized that alcoholic-derived oxidative stress is a major player in promoting inflammation and therefore serves as a potential therapeutic target. Recent studies demonstrate that oxidative stress could be regulated by the protein arginine methylation system.^(5,6)

Protein arginine methylation is a common post-translational modification that plays a role in multiple pathways, including cell cycle control, RNA processing, innate immune responses, apoptosis, oxidative stress responses, and other processes.

PRMT1 is a key enzyme responsible for about 85% of total cellular arginine methylations. It catalyzes arginine mono-methylation and di-methylation, which affects both histone and nonhistone proteins, thereby regulating gene transcription and splicing. Abnormal functions of PRMT1 have been implicated in various types of cancer including bladder, prostate, lung, and breast cancer in females.⁽⁷⁾

To examine the role of PRMT1 in the pathogenesis of alcohol-related HCC development, Zhao

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ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Cynthia Ju, Ph.D.
Department of Anesthesiology
IMcGovern Medical School
University of Texas Health Science Center at Houston
Houston, TX 77030
E-mail: changqing.ju@uth.tmc.edu
Tel.: +1-713-500-7424

et al. generated a mouse model of hepatocyte-specific PRMT1 deletion (PRMT1^{hep/}) by injecting an AAV-CRE vector to the PRMT1-floxed mice. Both wild-type (WT) and PRMT1^{hep/} mice were injected with DEN at 2 weeks of age and fed with alcohol (4.8%) from 6 months of age for 7 weeks to induce HCC. The data demonstrated that the PRMT1^{hep/} mice developed increased numbers of tumors compared with AAV-control treated WT mice. Interestingly, this increase was specific to alcohol-related HCC development, because PRMT1^{hep/} and WT mice had similar numbers of tumors when treated with DEN alone without the addition of alcohol feeding.

To understand the underlying mechanisms, the authors began by examining the role of PRMT1 in cell proliferation during HCC development. In contrast to the reported pro-proliferative function of PRMT1, they found that PRMT1 deficiency actually resulted in higher expression levels of proliferative genes (eg, cyclin D1 and WNT/b-catenin target genes). This finding suggested an indirect effect of PRMT1 and compelled the authors to examine liver-tissue inflammation and oxidative stress, which have been widely known to contribute to HCC development.

The subsequent studies revealed increased inflammatory markers, including a higher number of macrophages, chemokines and cytokines, as well as increased iNOS and reactive nitrogen species in PRMT1^{hep/} than WT mice. Moreover, PRMT1^{hep/} mice exhibited more severe liver injury and hepatocyte death due to the impaired expression of antioxidants, such as Sod1 and Sod2 proteins. However, it would be interesting to investigate whether depletion of PRMT1 in hepatocytes also affects other anti-oxidant enzymes, including catalase and glutathione peroxidase, which cooperatively regulate cellular oxidative stress and modulate cell viability. In addition, although the increased accumulation of monocyte-derived macrophages may contribute to the more severe tissue inflammation observed in the PRMT1^{hep/} mice, the role of Kupffer cells, which also express F4/80 and are known to be activated during alcohol consumption, remains unclear. Additional studies are warranted to understand the relative contributions and involvements of these two different hepatic macrophage populations.

PRMT1 is one of the major regulators of NO synthesis, as it has the ability to produce asymmetric-dimethylarginine, which has an inhibitory effect on iNOS.⁽⁷⁾ Consistent with this function of PRMT1,

the study showed that treatment of the PRMT1^{hep/} mice with an iNOS-selective inhibitor (1400W) significantly inhibited HCC growth and tissue inflammation/oxidative. However, a caveat is that the experiment does not provide direct evidence for the regulation of iNOS by PRMT1, as the treatment of an iNOS inhibitor is sufficient to inhibit HCC development, regardless of PRMT1 deletion. Therefore, further investigation is required to determine whether PRMT1 is directly involved in iNOS inhibition in alcohol-induced hepatic tumorigenesis.

In conclusion, the manuscript by Zhao et al. describes a function of PRMT1 in inhibiting HCC development caused by chronic alcohol consumption. The study reveals that PRMT1 inhibits alcohol-derived oxidative stress, specifically iNOS-derived NO, thereby reducing inflammation and suppressing tumor cell proliferation. Interestingly, a selective iNOS inhibitor (GW274150) and a general inhibitor (NG-monomethyl-L-arginine [L-NMMA]) are currently being evaluated in clinical trials for their therapeutic efficacy in inflammation-associated diseases (rheumatoid arthritis [NCT00370435] and asthma [NCT00273013]) and cancers (skin [(NCT03236935), lung [NCT03236935], breast [NCT02834403 and NCT04095689], and head and neck [NCT03236935]). This study provides evidence to explore the potential of targeting PRMT1 in the prevention and treatment of alcohol-related HCC. However, there are several questions raised by the current study that warrant further investigation.

Jong-Min Jeong, Ph.D.

Cynthia Ju, Ph.D.

Department of Anesthesiology

McGovern Medical School

University of Texas Health Science Center at
Houston

Houston, TX

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Author names in bold designate shared co-first authorship.