EDITORIAL OPEN ACCESS

Demethylase JMJD6 as a regulator of innate immunity in HCV-associated liver injury

Natalia A. Osna

Hepatitis C virus (HCV) infection causes the dysfunction of innate immunity in hepatocytes, the primary sites of viral replication. Anti-viral protection of hepatocytes requires the induction of interferon alpha (IFNα) signaling that activates interferon–stimulated genes (ISGs) to control viral replication and spread. The IFNα signaling is initiated by endogenous IFNα released by non-parenchymal liver cells (macrophages, dendritic cells) upon sensing the virus. Binding of IFNα to surface receptors on hepatocytes activates the JAK-STAT pathway. To attach to DNA and induce protective ISGs, STAT1 requires protein methyl transferase 1 (PRMT1)-mediated arginine methylation [1].

While protein expression level is regulated by histone methylation/acetylation, multiple methyltransferases induce the methylation of proteins on various residues (arginine, lysine, etc). In the liver, activities of many methyltransferases are regulated by the methionine metabolic pathway, namely, by the changes in the ratio between the methyl donor, S-adenosyl methionine (SAM) and its toxic metabolite, S-adenosylhomocysteine (SAH). Alcohol and HCV decreases SAM: SAH ratio [2–4], suggesting that SAM-dependent PRMT1 and subsequent STAT1 methylation in hepatocytes may be altered due to HCV- and alcohol-induced SAM insufficiency. Indeed, in infected hepatocytes, methylation of STAT1 on Arg-31 is impaired by HCV [5, 6]. Alcohol metabolites further decrease STAT1 methylation, thereby enhancing PIAS1-STAT1 interactions to prevent STAT1 binding to DNA [7]. Although suppression of STAT1 methylation was mainly attributed to PRMT1 dysfunction, we cannot exclude that HCV-induced demethylation of STAT1 also regulates IFNα signaling. In fact, it has been shown recently that the methylation of another innate immunity regulator, TNF receptor-associated factor 6 (TRAF6), is partially controlled by demethylase Jumonji domain-containing protein 6 (JMJD6) [8]. The JMJD6 is a non-heme Fe(II) 2-oxoglutarate (2OG)-dependent oxygenase with bifunctional enzymatic activities, arginine demethylase and lysyl hydroxylase [9, 10]. Importantly, STAT1 has never been characterized as a JMJD6 target, and the role of this enzyme in STAT1 methylation in hepatocytes has never been investigated in viral hepatitis.

In our laboratory, we studied whether arginine methylation of STAT1 is modulated by JMJD6 and whether there is a functional link between HCV replication and JMJD6 levels in IFNα-induced anti-viral protection via the JAK-STAT1 pathway in hepatocytes. The modulation of JMJD6 levels by viruses has been already demonstrated in literature [11, 12], but nothing is known about the role of JMJD6 in HCV-infection. In our preliminary (unpublished) experiments, we found that in Huh 7.5 (hepatoma) cells, JMJD6 overexpression reduced STAT1 methylation on arginine residue, while JMJD6 silencing increased STAT1 methylation. We also found that JMJD6 suppression enhanced activation ISGs and suppressed HCV RNA; however, there was a negative impact of JMJD6 overexpression on innate immunity (unpublished data). Previously, we indeed observed that impaired STAT1 methylation on both arginine and lysine residues of STAT1 contributed to the suppressed activation of ISGs by IFNα [7]. Surprisingly, JMJD6 provided no effect on lysine STAT1 methylation. The explanation of this discrepancy in JMJD6-induced regulation of arginine and lysine protein methylation is provided by another study demonstrating that JMJD3, but not JMJD6 was responsible for the lysine histone demethylation [13]. The results of our studies suggest that JMJD6 is one of the factors, which regulate HCV

Natalia A. Osna

Affiliations: Research Service, Veterans Affairs Nebraska-Western Iowa Health Care System, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA.

Corresponding Author: Natalia Osna, MD, PhD, Internal Medicine, UNMC, Veterans Affairs Nebraska-Western Iowa Health Care System, 4101 Woolworth Ave, Omaha, NE 68105, USA; Email: nosna@unmc.edu

Received: 17 May 2017
Published: 22 May 2017

infectivity levels in hepatocytes by suppressing ISG activation via the JAK-STAT1, the most important pathways for anti-viral innate immunity protection.

Thus, demethylase JMJD6 definitely plays an important role in the regulation of anti-HCV innate immunity. More studies are necessary to characterize JMJD6 contribution to HCV-infection pathogenesis and to identify other mechanisms by which JMJD6 may control the disease severity and outcomes. The role of this enzyme in the modulation of anti-viral protection makes JMJD6 an attractive target for the therapeutic interventions in viral hepatitis.

Keywords: Hepatitis C virus (HCV), Hepatocytes, Interferon–stimulated genes (ISGs), Jumonji domain-containing protein 6 (JMJD6)

How to cite this article

Osna NA. Demethylase JMJD6 as a regulator of innate immunity in HCV-associated liver injury. Int J Hepatobiliary Pancreat Dis 2017;7:15–17.

Article ID: 100067IJHPDNO2017

****

doi:10.5348/ijhpd-2017-67-ED-3

****

Author Contributions

Natalia A. Osna – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

Copyright

REFERENCES

1. Mowen KA, Tang J, Zhu W, et al. Arginine methylation of STAT1 modulates IFNalpha/beta-induced transcription. Cell 2001 Mar 9;104(5):731–41.
2. Kharbanda KK. Alcoholic liver disease and methionine metabolism. Seminars in Liver Disease 29(2):155–65.
3. Osna N, McVicker B, Poluektova L, Ganesan M, Kharbanda K. Mode of oral ethanol feeding affects liver oxidative stress levels and methylation status: Study on NS5A-transgenic Mice. International Journal of Biochemistry Research & Review 2014;4(4):344–57.
4. Osna NA, Bardag-Gorce F, White RL, Weinman SA, Donohue TM Jr, Kharbanda KK. Ethanol and hepatitis C virus suppress peptide-MHC class I presentation in hepatocytes by altering proteasome function. Alcohol Clin Exp Res 2012 Dec;36(12):2028–35.
5. Duong FH, Filipowicz M, Tripodi M, La Monica N, Heim MH. Hepatitis C virus inhibits interferon signaling through up-regulation of protein phosphatase 2A. Gastroenterology 2004 Jan;126(1):263–77.
6. Duong FHT, Christen V, Berke JM, Penna SH, Moradpour D, Heim MH. Upregulation of protein phosphatase 2Ac by hepatitis C virus modulates NS3 helicase activity through inhibition of protein arginine methyltransferase 1. J Virol 2005;79(24):15342–50.
7. Ganesan M, Zhang J, Bronich T, et al. Acetaldehyde accelerates HCV-induced impairment of innate immunity by suppressing methylation reactions in liver cells. American Journal of Physiology - Gastrointestinal and Liver Physiology Published 2015;309(7):G566–77.
8. Tikhanovich I, Kuravi S, Artigues A, et al. Dynamic arginine methylation of tumor necrosis factor (TNF) receptor-associated factor 6 regulates toll-like receptor signaling. J Biol Chem 2015 Sep 4;290(36):22236–49.
9. Chang B, Chen Y, Zhao Y, Bruick RK. JMJD6 is a histone arginine demethylase. Science 2007 Oct 19;318(5849):444–7.
10. Webby CJ, Wolf A, Gromak N, et al. Jmjd6 catalyses lysyl-hydroxylation of U2AF65, a protein associated with RNA splicing. Science 2009 Jul 3;325(5936):90–3.
11. Lawrence P, Pacheco J, Stenfeldt C, Arzt J, Rai DK, Rieder E. Pathogenesis and micro-anatomic characterization of a cell-adapted mutant foot-and-mouth disease virus in cattle: Impact of the Jumonji C-domain containing protein 6 (JMJD6) and route of inoculation. Virology 2016 May;492:108–17.
12. Chen CF, Feng X, Liao HY, et al. Regulation of T cell proliferation by JMJD6 and PDGF-BB during chronic hepatitis B infection. Sci Rep 2014 Sep 15;4:6359.
13. Salminen A, Kaarniranta K, Hiltunen M, Kauppinen A. Histone demethylase Jumonji D3 (JMJD3/KDM6B) at the nexus of epigenetic regulation of inflammation and the aging process. J Mol Med (Berl) 2014 Oct;92(10):1035–43.