Editorial

Deletion of tumor progression locus two attenuates alcohol-induced hepatic inflammation

Tao Han[1*], Guanggang Li[2*], Zhendong Zheng[1]

[1]Department of Oncology, Cancer center of People's Liberation Army, General Hospital of Shenyang, Shenyang 110840, China; [2]Affiliated Bayi Brain Hospital, PLA Army General Hospital, Beijing 100700, China

*These authors contributed equally to this work.

Correspondence to: Zhendong Zheng. Department of Oncology, PLA Cancer Center, General Hospital of Shenyang Military Region, No. 83, Wenhua Road, Shenhe District, Shenyang 110840, China. Email: zhengzhdong@163.com.

Comment on: Stice CP, Hussain S, Liu C, *et al.* Deletion of tumor progression locus 2 attenuates alcohol-induced hepatic inflammation. Hepatobiliary Surg Nutr 2016;5:29-37.

Submitted Sep 24, 2017. Accepted for publication Oct 17, 2017.
doi: 10.21037/tcr.2017.10.47
View this article at: http://dx.doi.org/10.21037/tcr.2017.10.47

Alcoholic liver disease (ALD) is the predominant cause of liver-related morbidity and mortality. Inflammatory cytokines, such as tumor necrosis factor-α and interferon-γ, inducing liver injury and lead to the development of ALD. The clinical manifestations are nausea, vomiting and jaundice, also lead to liver enlargement and painful, meanwhile, can be complicated by liver failure and upper gastrointestinal bleeding. Alcoholic hepatitis has a high independent risk of death more than inactive cirrhosis. A group of liver biopsy study found that the best prognosis of these patients is fatty liver, the 4–5 years of survival rate is 70% to 80%. The worst prognosis is alcoholic cirrhosis with alcoholic hepatitis patients, whose 4–5 years survival rate is 30% to 50%. And the prognosis of alcoholic hepatitis or cirrhosis patients is between the two, 4 to 5 years survival rate is 50% to 75% (1). The exact molecular mechanisms of the injury have not been elucidated yet. Tumor progression locus 2 (Tpl2) is a potent inflammatory mediator of serine/threonine protein kinase that regulates Th1 differentiation, drives the production of TNFα, and defense against intracellular pathogens of Toxoplasma gondii, listeria monocytogenes and mycobacterium tuberculosis (2). Tpl2 is closely related to tumor cell transformation and is overexpressed in lung cancer, breast cancer, endometrial carcinoma and colon cancer (3). However, there is relatively little known on the contribution of Tpl2 to ALD. In this manuscript, Dr. Camilla P. Stice *et al.* used TPL2KO mice to create alcohol-fed mouse model and then explore the role of TPL2 in it. They found that liver Tpl2 mRNA expression in the EtOH diet WT mice was significantly increased, and in the same time, indicated that the absence of TPL2 showed significant reductions in inflammatory cytokines, TNF alpha, IL-6 and IL-1 beta, and macrophage marker F4/80, reducing the number of inflammatory foci in the liver. Besides, they showed TPL2 deletion reduces hepatic steatosis and effect on phosphorylation of ERK and JNK, but neither of them reached statistical significance.

Chronic alcohol accumulation leads to liver damage, liver inflammation, fibrosis and hepatocellular carcinoma. However, effective therapy for ALD is still lacking. The pathophysiology of ALD is not entirely clear, but it is strongly associated with the direct toxic effects of alcohol and acetaldehyde, which is the main intermediate of alcohol (4). Cytokines such as interleukin IL-6, and IL-10 have also been mentioned in recent studies and been found to be related to ALD. IL-6 can activate STAT3 and induce a series of liver protective genes in liver cells to alleviate ALD. Alcohol stimulation increased intestinal endotoxin through the portosystemic shunt into the systemic circulation, and initiated Kupffer cells via lipopolysaccharide/Toll like receptor pathway 4, which lead to inflammatory diseases of liver (5). Anti-inflammation therapy has been found to be effective in the prevention of fibrosis. This suggests that blocking inflammation pathways could be a promising therapeutic option for patients with advanced fibrosis (6). It has been reported that TPL2, a regulator of inflammatory

pathways, played the modulatory role on CD3 + NK1.1 + iNKT signaling induced by lipid Ag (7). Furthermore, Cot/TPL2 KO mice exhibited reduced acetaminophen challenge after liver injury, such as decreased alanine and aspartate aminotransferase in serum (8). In this study, they firstly demonstrated EtOH diet could stimulates the expression of TPL2 and ablation of TPL2 reduced the hepatocyte inflammation under alcohol accumulation. It is of great novelty for them to choose TPL2, which was deeply involved with LPS/TLR4 pathways and up-regulated inflammatory cytokines. However, the results were just a supplement of relationship between TPL2 and hepatic injury. Hepatic steatosis is a significant characteristic of liver injury (9), yet a non-significant reduction in hepatic steatosis in this article is not convincible enough to explain the advantage of TPL2 deletion. The low sample size and variability of samples contributed to the lack of statistical significance, also it might owe to the regional distribution of steatosis, whereas a small amount of protein (approximately 50 g) for biochemical analysis does not represent the entire liver just as the author said. Moreover, TPL2 is a mitogen-activated protein kinase (MAPK) kinase kinase (MAP3K) that phosphorylates the MAPK kinases MEK1 and MEK2 (MEK1/2) (10), which, in turn, activate the MAPKs extracellular signal-regulated kinase 1 (ERK1) and ERK2 (ERK1/2) in macrophages stimulated through the interleukin-1 receptor (IL-1R), Toll-like receptors (TLRs), or the tumor necrosis factor receptor (TNFR) (11). The heterologous expression of MyD88 (L265P) in HEK293 cells resulted in phosphorylation of ERK1/2 MAPK in addition to NFκB activation, depended on the TPL2 activating downstream of the IKK complex (12). Surprisingly, compared with the control group, we found no significant statistical differences in ERK1/2 or JNK phosphorylation levels in alcoholic dietary mice. This is due to the major cell types of hepatocytes in the liver, which can explain the absence of significant discovery in downstream phosphorylated ERK1/2 and phosphorylated JNK and the need to analyze signals in specific cell types, rather than the entire liver tissue. In addition, another report pointed out that the proinflammatory effect of Tpl2 plays an important role in the pathogenesis of HCC (13).

Above all, this article expand our understanding of the function of TPL2 in alcohol-induced hepatic inflammation and the results may also help to better appreciate the novel approach to molecular targets for the prevention and treatment of ALD, but the mechanism is still inconsistent and need much further investigation in the future.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Xingshun Qi (Department of Gastroenterology, General Hospital of Shenyang Military Area, Shenyang, China).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2017.10.47). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Bellentani S. The epidemiology of non-alcoholic fatty liver disease. Liver Int 2017;37 Suppl 1:81-4.
2. Acuff NV, Li X, Latha K, et al. Tpl2 Promotes Innate Cell Recruitment and Effector T Cell Differentiation To Limit Citrobacter rodentium Burden and Dissemination. Infect Immun 2017;85. pii: e00193-17.
3. Gutmann S, Hinniger A, Fendrich G, et al. The Crystal Structure of Cancer Osaka Thyroid Kinase Reveals an Unexpected Kinase Domain Fold. J Biol Chem 2015;290:15210-8.
4. Takeuchi M, Takino JI, Sakasai-Sakai A, et al. Toxic AGE (TAGE) Theory for the Pathophysiology of the Onset/Progression of NAFLD and ALD. Nutrients 2017;9. pii: E634.
5. Soria-Castro I, Krzyzanowska A, Pelaéz ML, et al. Cot/tpl2 (MAP3K8) mediates myeloperoxidase activity and

hypernociception following peripheral inflammation. J Biol Chem 2010;285:33805-15.
6. Kawaratani H, Moriya K, Namisaki T, et al. Therapeutic strategies for alcoholic liver disease: Focusing on inflammation and fibrosis (Review). Int J Mol Med 2017;40:263-70.
7. Vyrla D, Nikolaidis G, Oakley F, et al. TPL2 Kinase Is a Crucial Signaling Factor and Mediator of NKT Effector Cytokine Expression in Immune-Mediated Liver Injury. J Immunol 2016;196:4298-310.
8. Sanz-Garcia C, Ferrer-Mayorga G, González-Rodríguez Á, et al. Sterile inflammation in acetaminophen-induced liver injury is mediated by Cot/tpl2. J Biol Chem 2013;288:15342-51.
9. Xu MJ, Zhou Z, Parker R, et al. Targeting inflammation for the treatment of alcoholic liver disease. Pharmacol Ther 2017;180:77-89.
10. Sanz-Garcia C, Sánchez Á, Contreras-Jurado C, et al. Map3k8 Modulates Monocyte State and Atherogenesis in ApoE-/- Mice. Arterioscler Thromb Vasc Biol 2017;37:237-46.
11. Senger K, Pham VC, Varfolomeev E, et al. The kinase TPL2 activates ERK and p38 signaling to promote neutrophilic inflammation. Sci Signal 2017;10. pii: eaah4273.
12. Rousseau S, Martel G. Gain-of-Function Mutations in the Toll-Like Receptor Pathway: TPL2-Mediated ERK1/ERK2 MAPK Activation, a Path to Tumorigenesis in Lymphoid Neoplasms? Front Cell Dev Biol 2016;4:50.
13. Li X, Liu C, Ip BC, et al. Tumor progression locus 2 ablation suppressed hepatocellular carcinoma development by inhibiting hepatic inflammation and steatosis in mice. J Exp Clin Cancer Res 2015;34:138.

Cite this article as: Han T, Li G, Zheng Z. Deletion of tumor progression locus two attenuates alcohol-induced hepatic inflammation. Transl Cancer Res 2017;6(Suppl 9):S1428-S1430. doi: 10.21037/tcr.2017.10.47

