The Multiple Modulation of miR-122 in the Attenuation of Alcoholic Liver Disease

Dear Editors:

I read with great interest for the article by Satishchandran et al.1 The authors have shown that the beneficial role of hepatic miR-122 in patients and mice with alcoholic liver disease (ALD) was modulated by grainyhead-like transcription factor 2 (GRHL2) to regulate hypoxia-inducible factor 1 alpha (HIF1α). However, the multiple effects of miR-122 on ALD remain worthwhile to investigate.

Recently, the regulation of hepatic lipid metabolism by miR-122 has attracted much attention. More studies focused on the role of miR-122 in nonalcoholic fatty liver disease than ALD. In contrast with the chemical stimulation of overnutrition in nonalcoholic fatty liver disease, ALD is induced by the chemical stimulation of ethanol. The critical feature of ALD is characterized by abnormal hepatic lipid accumulation related to ethanol metabolism and hypoxia response. As shown in the current report by Satishchandran et al,1 the deceased hepatic miR-122 expression accompanied by the increased liver triglycerides led to ALD severity. Nevertheless, the restoration of hepatic miR-122 or the inhibition of hepatic HIF1α rescued hepatic triglycerides and fibrosis for ALD. Conversely, the induction of HIF1α in mice with ALD had the ability to decrease lipid accumulation through interacting with target genes responsible for lipid metabolism.2

The controversial action of HIF1α relies on the complex modulation and transcriptional regulation by diverse cellular environment and multiple signals.

Interestingly, hypoxia-inducible factors linked to autophagy have not been well-reported in ALD. Generally, autophagy is involved in physiologic and pathophysiologic processes, and contains several sequential steps, including sequestration, degradation, and amino acid generation. The multifunctional modulation of autophagy affects ALD progress. Autophagy activation seemed to reduce acute ethanol-induced liver injury by removing damaged mitochondria and lipotoxicity.3 In contrast, autophagy suppression exacerbated liver damage and steatosis.4 Thus, the underlying mechanisms of miR-122 for the regulation of autophagy in ALD require more evidence and experiments to verify.

In addition, the amount of ethanol consumed and the duration of consumption have a great influence on hepatic miR-122 modulation in ALD. Chronic ethanol consumption rather than short-term ethanol consumption has been thought to alter hepatic miRNA expression and metabolism owing to ethanol adaptation.5 Ethanol-initiated hepatic inflammatory response and pathological process in ALD is complex. Under alcohol-induced liver injury, the down-regulation of hepatic miR-122 and inflammatory response were related to the release of tumor necrosis factor-α from Kupffer cells triggered by the binding of lipopolysaccharide to Toll-like receptor 4 (TLR4).6 Compared with hepatic miR-122, circulating miR-122 also exhibits as the biomarker for the evaluation of ALD. Based on the previous study by Bala et al,7 the increased serum alanine aminotransferase level was positively correlated with elevated serum miR-122 levels, whereas hepatic miR-122 expression was decreased in ALD. In addition, the increased circulating miR-122 was abrogated in TLR4-deficient (TLR4KO) mice, suggesting mediation via TLR4 activation. Thus, the analysis of circulating miR-122 expression level can provide a promising approach for a blood-based diagnosis of clinical ALD.

Collectively, although the modulation of miR-122 for target genes or receptors exhibits beneficial effects on the improvement of ALD progress and severity, the underlying roles of other miRNAs, gut hormones, and metabolic hormones involved in the ALD process are noteworthy.

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References


Conflicts of interest
The authors disclose no conflicts.

https://doi.org/10.1053/j.gastro.2018.02.036