Viewpoint

Hydrogen sulfide and nonalcoholic fatty liver disease

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Nonalcoholic fatty liver disease (NAFLD) is one of the most common chronic liver disease worldwide. The septum of NAFLD ranges from simple steatosis to nonalcoholic steatohepatitis, the latter of which may further progress to liver cirrhosis and even more advanced stages in 20% patients (1,2). During last decade, nonalcoholic steatohepatitis has been identified as the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the United States (3). Meanwhile, NAFLD also significantly increases risk of cardiovascular diseases, type 2 diabetes, chronic kidney disease, and colorectal neoplasia.

The pathogenesis of NAFLD has not been fully clarified (4). Hydrogen sulfide has been recognized as a toxic gas with the smell of rotten eggs for centuries. Recent studies (5-8) found that hydrogen sulfide regulates variety of physiological processes such as vasorelaxation, neuromodulation, and inflammatory responses. The liver is a major organ for endogenous hydrogen sulfide production and clearance, and there are increasing evidences indicating that hydrogen sulfide plays significant roles in physiology and pathophysiology of liver diseases (5). An early study found that endogenous hydrogen sulfide synthesis was impaired in cirrhotic livers (6). Subsequent studies found that hydrogen sulfide protected against hepatic ischemia/reperfusion injury and carbon tetrachloride-induced liver injury in rats (7,8).

The effects of hydrogen sulfide on regulation of hepatic lipid metabolism and NAFLD have also been intensively investigated. A recent study reported that hepatic hydrogen sulfide was significantly lower in the high fat diet-fed mice than that of controls (9). Another recent study reported similar results that hepatic hydrogen sulfide biosynthesis was impaired in methionine and choline deficient diet-induced rat model of NAFLD (10). Further mouse experiments showed that treatment with sodium hydrosulfide, a hydrogen sulfide donor, prevents nonalcoholic steatohepatitis by abating oxidative stress and suppressing inflammation (11). These studies highlight significant roles of hydrogen sulfide in NAFLD.

The reason for why hydrogen sulfide synthesis is impaired in NAFLD remains unclear. Hydrogen sulfide can be produced by pyridoxal-5'-phosphate (PLP)-dependent or PLP-independent enzymes in mammalian tissues. Cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) are PLP-dependent enzymes, and 3-mercaptopyruvate sulfurtransferase (MPST) is a PLP-independent enzyme utilizing 3-mercaptopyruvate as substrate to generate hydrogen sulfide (12). All these three enzymes express in the liver and regulate liver functions via hydrogen sulfide production. CBS/CSE system is considered to be responsible for the majority of endogenous hydrogen sulfide production, while MPST plays the aided action during hydrogen sulfide synthesis (13). It has been reported that the CBS/CSE system is highly expressed and active in the liver and has been proposed to serve as a potential therapeutic target for NAFLD (14). Nevertheless, the role of MPST in NAFLD has not been fully understood.

In a recent issue of *Gut*, Li *et al.* reported that hepatic MPST was significantly up-regulated in NAFLD patients

with predominant expression in steatotic hepatocytes (15). High fat diet-feeding or free fatty acids treatment also significantly up-regulated MPST expression in hepatocytes. Although MPST was up-regulated in the livers of high fat diet-fed mice and in free fatty acids-stimulated hepatocytes, hepatic hydrogen sulfide synthesis was impaired in these NAFLD models. In addition, knockdown of hepatic MPST significantly increased rather than inhibited hydrogen sulfide synthesis, and markedly ameliorated hepatocyte steatosis both *in vivo* and *in vitro*, while overexpression of MPST induced the opposite effects. Another important finding of Li's study is that their co-immunoprecipitation study found that MPST directly interacted with and negatively regulated CSE. Their mechanism experiments provided further evidences that hydrogen sulfide mediated the processing of suppressing SREBP-1 pathway, weakening JNK1 signaling and ameliorating hepatic oxidative stress, thereby contributing to the improvement of hepatocyte steatosis. These results suggested a significant role of MPST in NAFLD, and implied that MPST may be a potential therapeutic target for NAFLD.

It is undoubtful that hydrogen sulfide plays critical role in the pathogenesis of NAFLD. The study by Li *et al.* provided evidences for the first time that MPST, a PLP-independent enzyme catalyzing hydrogen sulfide production, is significantly involved in regulation of NAFLD. NAFLD includes a wide range of conditions spanning from simple steatosis to nonalcoholic steatohepatitis and even more severe stages. The current studies mainly focused on the role of hydrogen sulfide in simple steatosis. It would be of extreme importance to conduct further study to better elucidate the role of hydrogen sulfide and its catalyzing enzymes in the development and progression of NAFLD.

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Footnote

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