

Enteric dysbiosis, gut barrier and liver disease

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By employing the powerful animal model—Germ free mice and the development of the sequencing technology, gut microbiota nowadays has been recognized as a key pathophysiologic modulator for many diseases development, including liver injury progression. Intestinal microbial composition alteration, as well as functional disruption due to hepatotoxic agents challenge such as alcohol, fat or bile acids is recognized as the initial event during liver damage occurrence. Such dysbiotic status is complicated and is not fully understood yet. However, it is believed that the beneficial bacteria, also known as probiotics like *Lactobacillus* and *Akkermansia* were normally showed reduced abundance during liver injury progressions. Accordingly, supplementation of these bacteria into animals that underwent preclinical liver disease models exhibited alleviation phenotype. For example, *Akkermansia muciniphila* could markedly reduce both alcoholic and nonalcoholic fatty liver diseases (NAFLD) (1,2). *Lactobacillus rhamnosus* GG was able to improve both acute and chronic hepatotoxicity induced by ethanol (3,4). Other than single strain, the whole bacterial community seems to be more important for liver injury progression. Le Roy *et al.* found mice fed with high fat diet (HFD) exhibited differences in NAFLD symptom, they defined the mice showed more severe insulin resistance and hepatic steatohepatitis as “Responder” while those mice did not develop obvious NAFLD abnormalities were “non-Responder”. Germ-free mice received the feces from “Responder” displayed significantly increased hepatic triglyceride accumulation as well as higher fatty acid synthesis genes expression (5). Similarly, upon chronic alcohol consumption, transplantation of the feces from “Resistant” mice to “Sensitive” mice rescued “Sensitive”

mice from alcohol induced intestinal homeostasis disruption, hepatic steatosis and inflammation. Such fecal microbiota transplantation (FMT) is believed to be a novel and efficient therapeutic approach for liver disease (6). Indeed, Ren *et al.* already tried FMT for HBV patients; they found FMT is helpful for HBeAg clearance in the individuals that received long term anti-viral therapy with poor outcome (7). This interesting clinical observation encourages people to perform more translational studies to validate the beneficial roles of FMT in liver disease.

The detail mechanism for intestinal microbiota alteration during liver diseases development is still unclear. It is believed that host physiological disruption may be an important inducer. Specifically, during cholestatic liver injury, the intestinal bile acid profiles were completely altered and in response to this, bacterial growth was differentially modulated, finally lead to enteric dysbiosis. In addition, the antimicrobial proteins also played a key role, for example, chronic alcohol feeding markedly decreased intestinal *Reg3b* and *Reg3g* expression. These secreted C-type lectins deficiency in the gut resulted in microbial composition change, especially bacteria overgrowth and promoted bacteria translocation (8). Inflammasome was reported to be involved in NAFLD related dysbiosis. The bacterial composition alteration observed in *Asc^{-/-}* [apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (CARD)] mice was functionally transmittable (9). However, the detail mechanisms that disrupt gut microbiota balance during NAFLD were still poorly understood.

Once dysbiosis occurred, it may cause multiple different downstream pathophysiologic effects that promote liver

injury development. Gut barrier dysfunction, also known as gut leakiness was recognized as the main mediator. Bacteria and/or bacterial products such as LPS, PGN and DNA, known as pathogen associated molecular patterns (PAMPs) could penetrate from the lumen into circulatory system and liver to exhibit harmful effects. Gut barrier comprises four parts: (I) biological barrier: refers to the commensal microbiota located in the lumen, mucus layer and epithelial layer; (II) immunological barrier: refers to the immunity response related molecules such as IgA; (III) chemical barrier: refers to the secreted chemicals like bile acids and gastric acid; (IV) mechanical barrier: refers to the connection between intestinal epithelial cells. Mechanical barrier, especially for the tight junction was the determiner for the gut barrier function. The pathway that leads to gut permeability elevation was much clearer recently. We found chronic ethanol feeding firstly led to dysbiosis-linked intestinal inflammation as characterized by TNF-alpha overproduction, in turn, TNF-alpha from lamina propria could bind TNFR1 in the intestinal epithelial cell and activated MLCK, finally cause tight junctions expression disruption (10). Similarly, in bile duct ligation (BDL) induced liver fibrosis model, TLR2⁺ monocytes was activated and generated more TNF-alpha, further activated the RhoA signaling in the epithelial cell. LPS then translocated into liver to promote inflammation progression and fibrogenesis (11). Other than the inflammation, microbial metabolite is also involved in intestinal barrier maintenance and liver damage occurrence. We previously showed bacterial derived long chain saturated fatty acids exert protective effects on alcohol induced gut barrier dysfunction, mainly through enhancing the Lactobacillus abundance (12). Although the knowledge for the linkage between dysbiosis and leaky gut is growing, we are still standing far away from the truth. The direct action of microbiota and the microbial generated molecule on tight junctions' function is fully unknown and more attention has been paid to this novel field.

Enteric dysbiosis and gut barrier disruption are widely studied in chronic liver diseases model, including alcoholic liver disease (ALD) and NAFLD, however fewer studies have been performed on acute liver injury and end-stage liver diseases. This probably is the limitation for the current "Gut-Liver axis" theory. For acute liver injury, like drug induced liver injury (DILI) or septic liver injury, no available data revealed gut microbiota showed alteration compared with controls. Additionally, it seems to be difficult for gut microbiota to promote liver damage in such acute phase.

However, our unpublished data clearly demonstrated gut microbial generated dicarbonyl compound synergistically enhanced acetaminophen induced acute liver injury. This finding may tell us even in acute phase, gut microbiota may also drive liver damage development by some unknown molecule or pathways. For end-stage liver disease, it is recently reported that cirrhotic patient displayed alteration in microbiota composition compared with healthy controls (13). However, no further translational studies were reported. One possibility is that the enteric dysbiotic status in fibrotic or liver cancer individuals may be more complex than fatty liver patients. Future work may focus on this interesting field and it is confident to get positive outcome by employing "Gut-Liver axis".

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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