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Gut microbiota and drug-induced liver injury: an update

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The intestinal microbiota consists of trillions of microorganisms, most of which are considered to be nonpathogenic and play a defensive role in host immune system. Imbalance of the bacterial community has been associated with multiple host diseases, including fatty liver, metabolic syndromes, inflammatory bowel disease, and colon cancer. The liver is connected with the gut at both anatomical and physiological levels, and exposed to the products of the gut microbiota through the portal vein. Thus liver pathophysiology is closely influenced by the gut microbiota.

Drug-induced liver injury (DILI) presents a serious adverse drug reaction leading to liver dysfunction. It is a substantial health burden worldwide and the World Health Organization found that DILI is the fifth most common cause of liver disease-associated death. Studies suggested that drug-related metabolic process during DILI would lead to cellular oxidative stress, activation of inflammation, and eventually hepatocytes necrosis.[1] LiverTox, the National Institutes of Health-sponsored website on hepatotoxicity, has described more than 1200 agents (herbal products, antibiotics, chemotherapeutics, and immunomodulatory agents), which could potentially cause liver injury.[2] The pathophysiological process of DILI is complicated, little is known about the detailed mechanism of DILI. Currently, increasing evidence has revealed that the gut microbial function may contribute to drug-induced hepatotoxicity.

The gut microbiota has been reported to be able to influence the drug metabolisms, consequently influencing the drug efficacy and toxicity.[3] Gut microbial products may compete with drugs over the metabolizing process. *P*-cresol, for example, a product of gut microbiota, has been confirmed secreted by *Clostridium difficile*. Both *p*-cresol and acetaminophen (APAP) are recognized as the substrates for the sulfotransferase 1A1, and elevated production of *p*-cresol by gut microbiota reduces sulfonation of APAP, eventually leading to the accumulation of APAP in the liver.[4] Furthermore, bacterially-derived metabolites may directly modulate the expression of hepatic cytochrome p450 enzymes.[5]

We have recently reported the potential mechanism of the diurnal variation of APAP hepatotoxicity.[6] As known, the diurnal rhythmicity of microbiome is associated with host physiological states and diseases.[7] The study by Possamai *et al*[8] proved that variations in intestinal microbiota mediated the differential susceptibility to APAP hepatotoxicity. Our studies affirmed that zeitgeber time (ZT)12 (8:00 pm) group exhibited more severe liver damage than ZT0 (8:00 am) after APAP challenge in mice.[6] To explore how gut microbiota modulates APAP hepatotoxicity, 16S recombinant DNA (rDNA) analysis was performed at ZT0 and ZT12. The composition of gut microbiota was different between the two groups. Moreover, the metabolomics revealed that microbial metabolites, 1-phenyl-1,2-propanedione (PPD), could synergistically augment APAP induced liver damage. Intestinal bacterial strains such as *Escherichia coli* and *Citrobacter freundii* were confirmed to generate PPD. However, the beneficial microbiota, such as *Lactobacillus casei* and *Bacteroides thetaiotaomicron,* may not be able to produce PPD. PPD was demonstrated to directly deplete hepatic glutathione and accumulate more APAP-adducts. Our data provided a new piece of evidence to show the impact of gut microbiota on DILI based on the "gut microbiota-liver axis" concept.

Tacrine is a reversible acetylcholinesterase inhibitor to treat Alzheimer's dementia. The adverse effect of the drug is hepatic toxicity. Yip *et al*[9] reported that the intestinal microbiota contributes to the individual susceptibility to tacrine-induced hepatotoxicity. First, the authors classified the strong responder (StrR) (three times higher AST than the control group) and non-responder (NonR) groups in rats. They detected that the amount of total tacrine excreted in feces was higher in the StrR group than in the NonR group. Based on enterohepatic recycling, the author

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hypothesized that the secondary intestinal drug absorption (more deglucuronidated tacrine) was increased in StrR group and enhanced their susceptibility to hepatic toxicity. Further, they used 16S rDNA sequencing to profile the microbiome composition to check whether gut microbial functional changes were accompanied with tacrine-induced transaminitis. *Bacteroides* and *Enterobacteriaceae*, which have been known to exhibit β-glucuronidase activity were enrichment in the StrR group compared with the NonR group. Finally, the authors treated rats with β-glucuronidase or antibiotics before tacrine administration to confirm the association between microbiota and tacrine hepatotoxicity. After antibiotic treatment, the susceptibility to tacrine-induced hepatotoxicity was markedly decreased. Additionally, β-glucuronidase could enhance the potential liver damage induced by tacrine. This well-designed study provides a new piece of evidence that gut microbial activities directly influence DILI.

Recently, the interaction between herbal medicines and gut microbiota has been paid more attention. Administration of herbal medicines can directly affect the intestinal microbial composition. Gut microbiota can also "digest" herbal medicines by secreting digestive enzymes. Previous studies have also reported that gut microbiota could serve as a "medium" to transport compounds that are not absorbed by the intestinal tract.[10] Herbal medicines, such as Huanglian Jiedu decoction, can directly affect the intestinal short-chain fatty acids-producing microbiota.[11] *Lactobacillus*, *Bifidobacterium,* as well as their metabolic enzymes, such as β-glucosidase and α-rhamnosidase, participated in the deglycosylation progression of ginsenoside.[12] However, overdose administration of herbal medicines may cause liver injury. The relationship between the herbal medicines and gut microbiota needs to be further explored, and detailed mechanisms will provide a guideline in clinical.

Currently, the diagnosis and treatment of DILI are challenging, there are few specific diagnostic markers and specific treatment for DILI. In most cases, the sign of liver injury is the elevation of plasma aminotransferase level. Fecal microbial metabolite profiles may be different among various liver diseases.[13,14] Detecting microbial metabolites may be important and efficient for DILI diagnosis in the future. However, metabolomics studies are confronted with the challenge. Apart from the metabolites synthesized by microbiota, these metabolites can also be synthesized by the host. But with the progression of multi-omics technologies, the functions of gut microbiota will be further explained.

Another potential translational significance in this field is probiotics/prebiotics. Probiotics/prebiotics are employed as an effective approach for preventing and treating liver diseases. It may exert the therapeutic effects through the reconstruction of gut microbiota composition and modulation the host immunity.[15] The role of the probiotics/prebiotics in DILI need to be further defined.

In summary, growing evidence has disclosed the role of gut microbiota in the development of DILI. Targeting the gut microbiota-liver axis for the prevention of DILI progression and development is imperative in the future.

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Conflicts of interest

None.

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