

Editorial

Altered gut-liver axis in liver diseases[☆]

Chronic liver diseases have become a major global health problem and its prevalence has been rapidly rising during the last decade. Extensive studies have identified the major causes for the progression of these diseases including chronic viral infections, genetic mutations, excessive alcohol consumption, metabolic diseases, cholestatic liver injury and toxic effects of medications.^{1–3} Regardless of the aetiology, multiple common mechanisms, especially the gut-liver-axis, are associated with the pathogenesis and fibrotic disease progression of chronic liver injury. However, it remains challenging to develop effective therapeutics due to our limited understanding of these mechanisms. In this special issue, we are excited to present seven review articles and one original research paper. With this collection, we have provided the recent advances in understanding the roles of the gut-liver-axis in the development of a variety of liver diseases.

The liver is one of the largest immune organs in the body. The close anatomical proximity of the gut and the liver places the liver into the center of the interactions between the host and the gut microbiota. The review entitled “The role of gut microbiota in liver disease development and treatment”, written by Wang and Wan,⁴ summarizes the roles of gut microbiota in the development of liver diseases including liver cancer as well as gut microbiota-targeted therapies. It is well known that bile acids function as important signaling molecules in regulating lipid, glucose and energy metabolism. Recent studies have identified that in addition to farnesoid X receptor (FXR) and G protein-coupled receptor (GPCR) Takeda G protein-coupled receptor 5 (TGR5), another GPCR, sphingosine-1-phosphate receptor 2 (S1PR2) that is activated by conjugated bile acids is important in the regulation of hepatic metabolism and cholestatic liver injury.^{5–7} Maintaining bile acid and sphingolipid homeostasis is critical for normal physiological functions of not only the gut but also the liver.^{6,8} Some studies have shown that dysbiosis is closely linked with various liver diseases.^{9,10} The review article written by Kwong and Zhou¹¹ summarizes the recent understanding of sphingosine-1-phosphate (S1P)/bile acid-mediated activation of S1PRs in regulating gut barrier function and hepatic lipid metabolism. Development of chemical inhibitors targeting different S1PRs or sphingosine kinases represents a novel therapeutic strategy for both intestinal and liver diseases. The review article written by Wang *et al.*¹² further discusses the role of gut microbiota in the development of non-alcoholic fatty liver disease (NAFLD) with an emphasis on bile salt hydrolase in modulating the bile acid pool and FXR activation, which has been recently linked to ceramide-mediated signaling pathways in *de novo* lipid synthesis in the liver.

In addition to regulating the gut microbiota, bile acid-mediated signaling pathways are also important in gastrointestinal functions. The review article entitled “Bile acid receptors and gastrointestinal functions” by Ticho *et al.*¹³ summarizes the current knowledge of the functional roles of bile acid receptors in the gastrointestinal tract including electrolyte secretion and absorption, gastric emptying, and intestinal motility.

Cholangiopathies or cholestatic liver diseases comprise a large group of conditions in which injury is primarily focused on the bile duct epithelial cells, cholangiocytes. Accumulation of bile acids in the liver has been well documented as a major contributor to cholangiocyte injury.¹⁴ Recent clinical observations indicate that patients with primary sclerosing cholangitis (PSC) often have underlying inflammatory bowel disease.¹ The review article entitled “Functional roles of gut bacteria imbalance in cholangiopathies” by Sato *et al.*¹⁵ summarizes the current understandings of the functional roles of gut bacteria imbalance in cholangiopathies and suggests potential treatments by targeting gut bacteria.

Alcoholic liver disease (ALD) is one of the leading causes of cirrhosis and liver failure. The interaction between the microbiome and the host liver is of particular importance in ALD progression.^{16–19} Although it has been well-documented that inflammation plays a critical role in the development of ALD, the contribution of mast cells (MCs) to chronic liver diseases including ALD was only recognized recently.^{20,21} MCs are tissue-resident immune cells abundant in the gastrointestinal system that play diverse roles in regulating gut and liver functions. The review entitled “Alcoholic liver disease and mast cells: What’s your gut got to do with it?” by Tolefree *et al.*²² describes the recent findings regarding the role of MCs in the gut-liver axis with an emphasis on the interaction of MCs with microbiome in ALD.

Endoplasmic reticulum (ER) stress-induced the activation of a collection of conserved intracellular signaling pathways, the unfolded protein response (UPR), plays an important role in maintaining ER function for cell survival under stressed conditions.²³ However, prolonged activation of the UPR will result in cell death and tissue injury. During the last two decades, numerous studies have reported that ER stress is involved in almost all human diseases including many gastrointestinal and liver diseases. The review entitled “Endoplasmic reticulum stress and liver diseases” by Liu and Green²⁴ highlights recent findings that link ER stress and the UPR to the pathogenesis of liver diseases, including NAFLD, ALD, cholestatic liver disease and drug-induced liver injury.

Autophagy is an important and evolutionally conserved mechanism for maintaining cellular homeostasis and is closely related to the ER stress-induced apoptosis.²⁵ A growing body of evidence has shown that dysregulation of autophagy, either by over activation or

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inhibition, has been associated with various liver diseases.²⁶ In this special issue, Dr. Wen-Xing Ding's group reported that chlorpromazine, a dopamine inhibitor and a potent autophagy inducer, ameliorates acetaminophen-induced liver injury in mice by activating hepatic autophagy.²⁷

In summary, this special issue covers important topics of the gut-liver axis in the development of NAFLD, ALD, drug-induced liver injury, and cholangiopathies. Due to space limitations, we are unable to include viral hepatitis. The crosstalk between the gut and the liver has been increasingly recognized as an important factor in the development of various liver diseases. Identification of the key components in gut-liver interactions will provide important information to guide the development of novel target-based therapies.

Conflict of interest

The authors declare that they have no conflict of interest.

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