Gut Abnormalities: New Insights Into the Pathogenesis of Acetaminophen-Induced Liver Injury?

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Acetaminophen (APAP)-induced liver injury (AILI) is the leading cause of drug-associated acute liver failure in Western countries.[1] Currently, the hepatotoxic mechanism of APAP is mainly focused on the liver; more than 90% of absorbed APAP is passed through the liver where it is sulfated and glucuronidated. The remaining unmodified APAP is transformed into *N*-acetyl-*p*-benzoquinone imine (NAPQI) by cytochromes P450. NAPQI can be further detoxified by glutathione (GSH). Upon GSH depletion, excess NAPQI modulates protein structures and induces mitochondrial dysfunctions, mediating hepatocyte death, dysregulation of immune responses, and liver damage.[2,3] Although this pathway is well recognized, the factors mediating APAP-associated cytotoxicity, especially in extrahepatic tissues, remain unknown.

In this issue of *Hepatology Communications*, Chopyk and colleagues[4] report on the roles of intestinal injury during AILI. They found that APAP administration dramatically increased gut leakiness and intestinal epithelial cell apoptosis. These detrimental events in the intestine were accompanied by leucine-rich repeat-containing G protein-coupled receptor 5 (LGR5)-positive stem cell death. Although these descriptive results did not provide more mechanistic insights, the authors excluded two possibilities suggested. First, mice treated with APAP, which showed increased intestinal permeability, did not exhibit augmented hepatocyte apoptosis, indicating that hepatocyte apoptosis did not contribute to AILI in the animal model. Thus, this article further strengthened the hypothesis that necrosis may be the main cell death type during AILI progression.

Second, although it has been reported that increased intestinal permeability during liver injury is attributed to tumor necrosis factor (TNF) signaling activation in epithelial cells,[5,6] the authors found that APAP-linked gut leakiness was independent of TNF signaling. Other potential mediators may be involved. Our current unpublished data suggest that chemokine overexpression, such as chemokine (C-C motif) ligand 7 (CCL7) in epithelial cells, is associated with gut leakiness and bacterial product translocation during AILI. Thus, together with the findings from Chopyk and colleagues, inflammatory factors produced from apoptotic epithelial cells as well as crypt cells may serve as key contributors for intestinal barrier dysfunction after APAP acute challenge.

This novel finding is significant in that it directly associates gut barrier disruption with AILI. In the clinic, patients with liver transplantation due to APAP overdose have higher 30-day mortality rates than non-APAP cases.[7] Therefore, gut leakiness, which leads

Abbreviations: AILI, acetaminophen-induced liver injury; APAP, acetaminophen; NAPQI, N-acetyl-p-benzoquinone imine.

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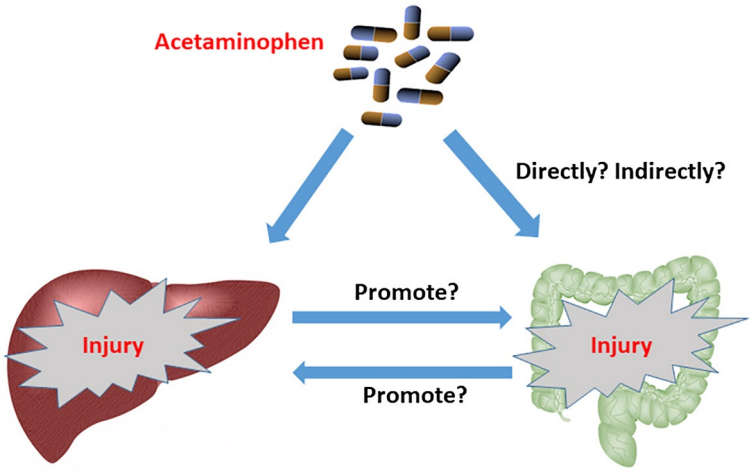

FIG. 1. Potential crosstalk between the liver and intestine during AILI.

to translocation of intestinal microbiota or microbial products, could partially contribute to this phenomenon. In addition to this translational significance, this new piece of evidence suggests that intestinal injury may be important for AILI progression. Researchers in this field should pay more attention to the gut and the novel concept of the pathogenesis of AILI and its related complications.

There are still questions regarding the intestinal injury and AILI progression mechanism. First, it is unclear how APAP causes intestinal cell death in such an acute phase (Fig. 1). Is it the consequence of the direct response of epithelial cells to the drug or the indirect crosstalk between the liver and gut during hepatotoxicity development? If it is indirectly caused, what are the mediators modulating cell death? Second, in addition to cell apoptosis in the gut, what other mechanisms, such as inflammatory factors or tight junction disruption, may be involved in the occurrence of gut leakiness? Finally, could a novel treatment strategy be developed for AILI based on this new concept? These questions might be addressed by future investigations.

Overall, by identifying the intestine as a novel target, the Chopyk et al. study helps put the pathogenesis of AILI in perspective. It also further strengthens the importance of the gut in the progression of liver disease.

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