The Great Escape: Microbital LPS Takes a Toll on the Liver

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Abstract

The interaction between the intestinal microbiota and host is much more complex than previously appreciated, and we are now learning that it can have an impact on extraintestinal human diseases. In this issue of the journal (beginning on page 1090), Lin and colleagues present important data linking the microbiota, lipopolysaccharide (LPS), and toll-like receptor (TLR)4 with hepatitis in a mouse model. These provocative results and those from other recent studies highlight the microbiota as a potential target for therapeutic intervention in several liver diseases. Cancer Prev Res; 5(9); 1078–80. ©2012 AACR.
model of hepatocellular carcinoma (HCC; ref. 8). Genetic deletion of IKKβ in myeloid cells and hepatocytes, a signaling protein upstream of NF-κB, attenuated disease in a chemical model using diethylnitrosamine (DEN) to induce liver damage and HCC (9). Two studies have shown a role for MyD88 in liver disease; Ojio and colleagues using the ConA hepatitis model (10) and Naugler and colleagues who showed that deficiency in MyD88 led to a decrease in HCC in the DEN model (11). Furthermore, Naugler and colleagues linked disease to production of the downstream proinflammatory cytokine IL-6, that was essential for HCC (11). This supports the current data from Lin and colleagues, who show that TLR4 is critical for IL-6 production in the ConA model of hepatitis (7). Together, these studies identified the TLR4/MyD88/NF-κB axis as playing a role in specific liver diseases/conditions, but did not study the source of the ligands that activated this pathway. This link was first shown by Seki and colleagues, who used a bile duct ligation model of liver injury to show that the microbiota signaling through TLR4 and MyD88 promote liver inflammation and fibrosis (12). Dapito and colleagues showed that the microbiota promote HCC through activation of TLR4 using a DEN/CCL4 model (13); although in this latter study, the investigators actually found slightly increased liver injury in the TLR4-deficient mice, reflecting the complexity of outcomes depending on the context in which this signaling occurs. Together, these studies elegantly show the role of the microbiota and the TLR4/MyD88/NF-κB axis in models of liver disease (7, 12, 13).

Interestingly, the link between TLR4 and liver disease is supported by genetic data from humans. A TLR4 polymorphism was identified as part of a genetic signature that is predictive of decreased risk of development of cirrhosis (14). This polymorphism results in a compromised TLR4 that is attenuated for signaling in response to LPS (15). Further supporting the link between LPS, TLR4, and liver disease in humans, is evidence that patients with cirrhosis have higher levels of LPS in their blood (16). Together, data from clinical studies and animal models strongly indicate that recognition of microbiota LPS by TLR4 contributes to diverse liver diseases.

Because TLR4 can promote liver disease, an interesting question is whether other innate immune receptors, including other TLRs, are involved as well. Bacteria contain numerous MAMPs, so it is logical that other ligands, in addition to LPS, could contribute to liver inflammation and pathology. In fact, using the bile duct ligation model, Miura and colleagues showed a critical role for LIR9 in liver fibrosis (17). In this context, TLR9 presumably signals in response to bacterial DNA derived from the intestinal microbiota. Using the same model, another study found no role for TLR2 in the fibrotic response (12). Interestingly, TLR3 has been shown to be involved in promoting hepatitis using the ConA model, although no link to the microbiota was shown in this study (18). TLR3 can respond to double-stranded RNA from viruses, but the authors suggest that TLR3 may be activated in response to the release of nucleic acids from damaged or dying liver cells in this model (18). In addition to TLRs, many other innate receptors recognize microbes and play a role in inflammatory responses. NLRs (Nod-like receptors) initiate the activation of cytosolic protein complexes called inflammasomes that lead to the secretion of the proinflammatory cytokines IL-1β and IL-18 (19). These cytosolic receptors can play a role in intestinal inflammatory conditions such as colitis (20), and it will be interesting to determine whether they are involved in the response of the liver to translocated bacteria/MAMPs and subsequent liver diseases.

Another important question is which factors lead to increased intestinal permeability and bacteria/MAMP translocation, as these are the initial events that subsequently lead to TLR signaling and accelerated inflammation in the liver. This phenomenon may be linked to decreased intestinal motility, intestinal bacterial overgrowth, mucosal oxidative stress, intestinal inflammation, portal hypertension, and/or compromised tight junctions, and further studies will be required to evaluate the relative contributions of these diverse factors (6). A greater understanding of the molecular mechanisms that lead to altered permeability will hopefully facilitate therapeutic interventions. Proteins whose activity may promote increased intestinal permeability include JAM-A (21) and the nonmuscle form of myosin light chain kinase (MLCK; ref. 22). LPS-induced intestinal permeability was inhibited by an MLCK inhibitor in rats (23). Furthermore, transgenic mice expressing constitutively active MLCK in intestinal epithelial cells exhibit tight junction dysfunction and increased basal immune activation (22). It may be instructive to use this genetic model to examine the role of increased bacteria/MAMP translocation in liver disease and study whether intestinal barrier dysfunction alone predisposes mice to such diseases.

Because many liver diseases develop chronically, it is important to understand at what stage translocated bacteria/MAMPs and innate signaling play a role. HCC, like other cancers, depends on an initiating mutational event as well as potentiating events that lead to progression. Pikarsky and colleagues, using the Mdr2 model, found that NF-κB promoted HCC progression, but not its initiation (8). In agreement, Dapito and colleagues showed elegantly using the DEN/CCL4 model that the microbiota and TLR4 contribute specifically to the progression of HCC (13). In fact, by using antibiotics to eliminate the microbiota, the authors show that progression to HCC can be inhibited by as much as 90%. Collectively, these remarkable results highlight the fact that therapeutics targeting the microbiota or preventing bacteria/MAMP translocation or inflammatory signaling may be able to prevent the progression of some cancers before they have a significant effect on human health.

The prospect of stifling some cancers by eliminating the microbiota is exciting, but this approach would likely have deleterious long-term health consequences. Similarly, drugs that inhibit TLR4 or other innate immune signaling components may have beneficial effects on certain liver diseases, but it is not clear whether they would be tolerated long-term as they would likely have a negative impact on innate health.
immune function and defense against infection. Perhaps the most benign yet potentially effective strategy would be to alter the makeup of the intestinal microbiota. Recent studies suggest that the microbiota contains both beneficial and potentially harmful bacteria and that an incorrectly balanced microbiota can contribute to disease (6). As this exciting area is explored in greater detail, we will learn which specific bacteria are beneficial or detrimental and through the use of probiotics or dietary changes (which can alter the microbiota), may be able to harness this information to reverse the chronic low-grade inflammatory state thought to occur in the diseased liver, and thereby prevent the progression to severe diseases such as HCC.

References


Disclosure of Potential Conflicts of Interest

The contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. No potential conflicts of interest were disclosed.

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