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Microbiota in promoting liver regeneration

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Extensive work has revealed well-coordinated mechanisms that underlie liver regeneration, albeit with a focus on intrinsic interactions within hepatic cells. Here, Hess et al.[1] demonstrate that *Mycobacterium leprae* infection can induce liver growth of nine-banded armadillo without obvious side effects.

The liver is a pivotal organ to maintain metabolic homeostasis. A unique feature of the liver is its remarkable capacity to regenerate efficiently upon various injuries, which is considered an evolutionary adaptive response to the constant exposure to the inflow of ingested toxins. Liver regeneration is a highly orchestrated cellular response associated with signaling cascades involving sequential gene activation, growth factor production, and tissue remodeling, which have been extensively studied and reviewed.[2,3] Most research on liver regeneration has typically focused on signaling pathways within hepatic cells. However, an array of evidence also suggests that gut microbiota may significantly regulate liver regeneration. Previous studies demonstrated that liver regeneration was delayed after partial hepatectomy in germ-free, or lipopolysaccharide (LPS)-resistant rodents.[4] Depletion of gut commensal bacteria by oral ampicillin treatment impaired mouse liver regeneration by breaking hepatic innate immune tolerance and inducing hyperactivation of hepatic NKT cells, an immune cell population impeding liver regeneration.[5] The gut microbiota can stimulate liver regeneration through multiple mechanisms. For example, gut-derived LPS has complex effects on liver injury and regeneration. LPS can enhance liver regeneration by stimulating the expression of tumor necrosis factor alpha and interleukin-6 in Kupffer cells through Toll-like receptor 4 signaling after partial hepatectomy, an injury relatively free of inflammation.[6] On the other hand, LPS can also aggravate liver injuries and impair liver regeneration under complex injury scenarios with a strong inflammatory reaction, such as acetaminophen-induced liver injury.[7] In addition, bile acids, another key metabolic signal involved in liver regeneration, are tightly regulated by both host and microbiota through enterohepatic circulation. Bile acid spillover to the systemic circulation after partial hepatectomy is necessary for efficient liver regeneration.[8] Such findings suggest a significant impact of the gut microbiota on liver regeneration, which is still far from fully understood.

In this issue of *Cell Reports Medicine*, an interesting study found that *Mycobacterium leprae* (ML) infection could induce profound liver growth of nine-banded armadillo without obvious side effects. The authors initially found that ML infection can reprogram adult Schwann cells into a stem cell-like stage to facilitate infection dissemination.[9] Then, the authors reasoned that ML might exploit the same strategies to reprogram and expand host cells in other highly regenerative tissues, such as the liver, *in vivo* during natural infection. Consistently, they found that ML infection reactivated liver progenitor markers and liver regeneration-associated genes, similar to the rodent hepatectomy model. Importantly, the regenerative liver showed normal zonation and functional metabolic marker expression, without fibrosis and tumorigenesis.[1] ML infection-induced liver regeneration in nine-banded armadillo may provide a new platform for studying the underlying mechanisms and for developing a better way to promote regenerative therapies for liver injury. Hepatectomy studies point toward the existence of a "hepatostat" that maintains liver size to 100% of what is required for homeostasis. As hepatocytes can respond to liver volume loss extremely fast, it is tempting to view hepatostat as a delicate balance between pro-regenerative and anti-regenerative mechanisms. ML infection may hijack pro-regenerative clue and slightly shift the balance toward regeneration without causing obvious side effects. The detailed mechanism of ML infection-induced liver regeneration required further investigation.

The liver is traditionally regarded as a sterile organ. However, a very recent study demonstrated that the liver of both mice and humans harbors a microbiota, which is distinct from that of the gut.[10] This study suggested that the liver microbiota has dramatic impacts on liver immunity by modulating inflammatory cell recruitment and maturation through their microbiome-derived glycosphingolipids. The influence of this naive liver microbiota on liver regeneration is unknown. However, this finding reminds researchers to consider the effects of the microbiota on liver regeneration in more complex scenarios.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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