

Effect of gut bacteria on specific immune cells underlies persistent liver inflammation

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Persistent liver inflammation in sufferers of chronic viral hepatitis is likely caused by interactions between pro-inflammatory immune cells in the liver and products from gut bacteria, according to new work involving A*STAR researchers. The findings identify new therapeutic targets.

Chronic viral hepatitis is characterized by [persistent inflammation](#) of the liver, but the mechanism that maintains this [inflammation](#) has been poorly understood. The degree of inflammation does not correspond to the extent of viral activity in the liver, or to the activity of [immune cells](#) that specifically target the virus, as might be expected.

The new work, a collaboration between the laboratories of Antonio Bertoletti at the Duke-NUS Medical and Singapore Institute of Clinical Sciences, the laboratory of Qingfeng Chen at the A*STAR Institute of Molecular and Cell Biology and Charles-Antoine Dutertre in the laboratory of Florent Ginhoux from the A*STAR Singapore Immunology Network, aimed to determine the mechanisms underpinning the inflammation. The researchers focused on a different group of immune cells called [macrophages](#), which are increasingly recognized as significant in [liver disease](#).

They analyzed the molecular and functional profiles of macrophages in the livers of patients with chronic viral hepatitis and those of healthy people. In the livers of patients, there was an excess of macrophages with a specific profile that promotes inflammation. "Unlike

macrophages found in a healthy liver, these macrophages have the capacity to continuously produce pro-inflammatory mediators when they encounter bacterial products," explains Dutertre.

The team studied this phenomenon further in mice engineered to have human liver cells and [human immune cells](#). The mice were infected with hepatitis B virus, and consequently accumulated the same pro-inflammatory macrophage population in the liver as that seen in patients. Treatment of the mice with antibiotics to reduce the [gut bacteria](#) reversed the accumulation of these macrophages. "This demonstrated that bacterial products that leak from the gut into the liver are responsible for the accumulation of the pro-inflammatory macrophages," says Dutertre.

The results identify a novel mechanism that maintains inflammation in chronic viral hepatitis. Dutertre and colleagues say that their findings suggest new therapeutic approaches, in addition to targeting the virus, that involve modifying the intestinal bacteria or depleting the pro-inflammatory macrophages in the liver.

The researchers are now investigating the mechanism behind the effects of bacterial products on macrophages in the liver. So far they have identified certain soluble mediators that play a pivotal role. "Our hypothesis is that by inhibiting these soluble mediators, we could limit the accumulation of the pro-inflammatory macrophages and resolve [liver](#) inflammation in patients with chronic viral hepatitis," concludes Dutertre.

More information: Alfonso Tan-Garcia et al. Intrahepatic CD206 + macrophages contribute to inflammation in advanced viral-related liver disease, *Journal of Hepatology* (2017). [DOI: 10.1016/j.jhep.2017.04.023](https://doi.org/10.1016/j.jhep.2017.04.023)

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