Elevated lymphotoxin expression in liver leads to chronic hepatitis and causes HCC

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A recent study maps the pathway that leads from infection with Hepatitis B and C virus (HBV and HCV) to chronic hepatitis and liver cancer and proposes a new therapeutic strategy for treating liver diseases with chronic inflammation. The research, published by Cell Press in the October issue of the journal *Cancer Cell*, describes a signaling pathway that can be beneficial during liver regeneration, but can lead to chronic hepatitis and severe liver damage when chronically activated. The research was performed in the Department of Pathology, Institutes of Clinical Pathology and Neuropathology at the University Hospital in Zurich.

HBV and HCV cause chronic hepatitis and can lead to hepatocellular carcinoma (HCC), the most prevalent primary liver cancer in humans. "Although aberrant expression of cytotoxic cytokines is thought to be critically involved in hepatitis-induced liver cancer, the exact mechanisms driving this progression remain elusive," explains senior study author Dr. Mathias Heikenwalder.

The cytokines lymphotoxin (LT) alpha and beta are mainly produced by white blood cells called lymphocytes and play an important role in organ development and control of the immune response. Previous work had shown that, when compared with normal livers, HCV-infected livers exhibit dramatically increased expression of LTbeta. Dr. Heikenwalder's laboratory, in collaboration with the laboratory of Professor Adriano Aguzzi and colleagues investigated a possible causal relationship between aberrant sustained hepatic LTalpha signaling, chronic hepatitis

and the development of HCC.

The researchers found that LTalpha, LTbeta and the LT receptor (LTbetaR) were upregulated in HBV- or HCV-induced hepatitis and HCC and identified both lymphocytes and liver cells called hepatocytes as the main expressing cells. Liver specific expression of LTalpha and LTbeta induced chronic liver inflammation and HCC in mice. It was the hepatocytes themselves which were the major LT-responsive liver cells and, importantly, when LT?R signaling was blocked in mice with chronic hepatitis, inflammation was partially attenuated and HCC was prevented.

It appears as if LTbetaR signaling might be beneficial in some cases and detrimental in others. Previous work has shown that LTbetaR signaling in liver cells supported liver regeneration. However, as is evidenced in this study, there is a causal link between chronic LTbetaR signaling and both chronic hepatitis and HCC development.

Taken together, the findings indicate that sustained LT?R signaling in liver leads to chronic hepatitis-induced HCC. "Our results show that LT signaling is critically involved in the development of chronic hepatitis and subsequent HCC formation and imply that blocking LTbetaR signaling might become a beneficial therapeutic approach in the context of HBV- or HCV-induced chronic hepatitis and other liver diseases displaying sustained hepatic LTbetaR signaling," concludes Dr. Heikenwalder.

Source: Cell Press (news : web)

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