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Unappreciated role of type-I interferon signaling in HBV and HCV persistent infections and resistance to interferon therapy

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Activation of the type-I interferon (IFN) signaling pathway poses the first line of defense against many virus infections, including HCV and HBV. With the activation of the Jak/STAT signaling leading to the increased expression of several hundred interferon-stimulated genes (ISGs) in the liver microenvironment, an anti-viral state was established and the virus replication was suppressed. However, over-activation of the type-I IFN signaling may actually benefit virus leading to its persistent infection. High throughput gene expression profiling identified 18 differentially-expressed hepatic genes between treatment responders (Rs) and non-responders (NRs) to IFN treatment of patients chronically infected with HCV. Many of these genes are ISGs and they all showed higher expression levels in the pretreatment liver tissues of NRs, indicating that over-activation of type I IFN signaling contributes to treatment non-response leading to persistent infection. Similar findings were observed in chronic HBV infection. Mechanistically, some of these ISGs, such as ISG15 and ISG16 stimulated HCV replication and blunted IFN anti-HCV activity. In line with our observations, studies from other labs demonstrated that blocking IFN signaling facilitated viral clearance in chronic infections, such as in LCMV. All these data point out that type-I IFN signaling is a "double-edged" sword, while activation of this pathway is indeed necessary to control viral spread, over-activation actually benefits virus to facilitate its persistent infection. Detailed molecular mechanisms warrant further investigation.

Biography

Limin Chen is a Professor in the Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC) and also an Affiliate Scientist with the University of Toronto. He is now the Director and Chief Scientific Officer of the Center for Transfusion Transmitted Diseases, Institute of Blood Transfusion (IBT), CAMS/PUMC, Member of the American Association for Studies of Liver Diseases (AASLD) and Canadian Association for Studies of Liver (CASL). He obtained his MD, MSc in Biochemistry and Molecular Biology in China, PhD in Molecular Genetics at the University of Toronto. He obtained his Postdoctoral training both at the Merck Research Laboratories and at the Harvard Medical School. Currently, his research focuses on the virus-host interaction of the hepatitis viruses, especially HCV. He pioneered the work on identification of the response signature and proposed a novel mechanism on how HCV exploits host innate immune response to benefit its persistent infection and resistance to interferon-based therapy.

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