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Novel insights into the molecular mechanisms of interferon resistance of hepatitis C and B viruses based on gene expression profiling

Hepatitis viruses, including Hepatitis B virus (HBV) and Hepatitis C virus (HCV) infect human liver leading to chronic infections that gradually develop into cirrhosis and hepatocellular carcinoma (HCC). Current treatment regimen includes interferon and nucleotide analogues (NAs). Although direct acting anti-viral agents (DAAs) clear the virus in more than 95% individuals chronically infected with HCV, pegylated interferon is still widely used in many Asian countries. Unfortunately, not all patients chronically infected with HCV respond to pegylated interferon/ribavirin combination therapy. As such, understanding the molecular mechanisms of interferon resistance of HCV and HBV is essential for better management of patients. Based on gene expression profiling, we identified an 18-gene response signature that can be used to predict whether a given patients will respond to interferon-based therapy with an accuracy of 96%. A novel ubiquitin-like ISG15/USP18 signaling pathway was also identified to be involved in interferon resistance in both HCV and HBV infections. A series of functional studies on ISG15 and USP18 genes revealed the detailed molecular mechanisms of interferon resistance of HBV and HCV. Data from our studies indicated that ISG15 (and ISG15 conjugation-the process called ISGylation) stimulated HCV replication and potentiated the interferon anti-HCV activity. Silencing of USP18 boosts the antiviral activity of interferon against hepatitis C virus infection through activation of the Jak/STAT signaling in vitro HCV culture (HCVcc) model.

Biography

Limin Chen is serving as a Professor with the Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC) and also an Affiliated Scientist with the University of Toronto. Currently, he is 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 and MSc in Biochemistry and Molecular Biology in China and PhD in Molecular Genetics at the University of Toronto. He obtained his Post-doctoral 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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