proceedings

MDPI

Abstract

Interferon-Stimulated SAMHD1 Restricts Hepatitis C Virus Replication †

Ni An *, Jianyuan Zhao and Shan Cen

Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences, Beijing 100730, China; zjyuan815@163.com (J.Z.); shancen@hotmail.com (S.C.)

* Correspondence: pumcann@163.com

† Presented at Viruses 2020—Novel Concepts in Virology, Barcelona, Spain, 5–7 February 2020.

Published: 13 June 2020

Abstract: Human SAMHD1 is an IFN-induced dNTP triphosphatase that is able to restrict HIV-1 replication, whereas its role in innate immunity against virus infection remains largely unexplored. In this work, we provided evidence that SAMHD1 functions as an anti-HCV host factor. We found that overexpression of *SAMHD1* resulted in significant inhibition on the replication of HCV, but not other RNA viruses including influenza A virus and EV71. SAMHD1 knockdown partially relieved the inhibitory effect of IFN on HCV, suggesting its important role in the innate immune response against HCV. Mechanistic studies revealed that SAMHD1 targets viral RNA replication without impact on both protein translation and virus entry. Transcriptome analysis showed a broad inhibitory effect of SAMHD1 on host genes involved in cholesterol and fatty acid biosynthesis. In particular, SAMHD1 was shown to downregulate the mRNA abundance of *SREBP1*, a master transcriptional regulator of de novo lipid biosynthesis, impairing the formation of lipid droplets. Restoring intracellular lipid levels by either exogenous lipid addition or *SREBP1* overexpression counteracted the restriction of HCV by SAMHD1, providing evidence that SAMHD1 inhibits the replication of HCV by suppressing host cholesterol and fatty acid biosynthesis. Together, these data unveil, for the first time, a novel antiviral mechanism of SAMHD1 and open new avenues for the development of novel anti-HCV therapeutics.

Keywords: *SAMHD1*; HCV; lipid droplets