Hepatitis C Virus and Protein Degradation System

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Abstract
Hepatitis C virus (HCV) is a single-stranded, positive-sense RNA virus that is classified in the family Flaviviridae. HCV is the main cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. More than 170 million people worldwide are chronically infected with HCV. The approximately 9.6-kb HCV genome encodes a unique open reading frame that is translated into a polyprotein. The polyprotein is cleaved cotranslationally into at least 10 proteins by viral proteases and cellular signalases. There is growing evidence suggesting that the ubiquitin-proteasome pathway and the ubiquitin-independent proteasome pathway are involved in the stability control of HCV proteins. Many viruses manipulate the proteasome pathways to modulate the cell cycle, inhibit apoptosis, evade the immune system, and activate cell signaling, thereby contributing to persistent infection and viral carcinogenesis. The identification of functional interactions between HCV and the proteasome pathways will gain a better understanding of the life cycle and pathogenesis of HCV.

We previously reported that the HCV core protein is degraded through the ubiquitin-proteasome pathway. We discovered that the cellular ubiquitin ligase E6AP is involved in ubiquitylation and degradation of HCV core protein. Our results suggest that E6AP-mediated ubiquitin proteasome pathway affects the production of HCV particles through controlling the amounts of HCV core protein. On the other hand, PA28gamma, a REG family proteasome activator, was identified as another regulatory factor for the turnover of the HCV core protein. PA28gamma enhances the proteasomal degradation of the HCV core protein in an ubiquitin-independent manner. The stability of HCV proteins is regulated by ubiquitin-proteasome system and ubiquitin-independent proteasome pathway.

HCV NS5A protein is a major component of HCV replication complexes and plays an essential role in viral replication. The stability of the NS5A protein is also regulated through the ubiquitin proteasome pathway. We have identified an E3 ubiquitin ligase as a novel NS5A-binding protein. We are currently investigating a role of the E3 ligase in HCV life cycle. In this seminar, I will discuss the roles of the proteasome pathways in HCV life cycle as well as in viral pathogenesis.

About our Speaker…
Since 2007 Associate Professor Ikuo Shoji has been working with the Division of Microbiology, Kobe University Graduate School of Medicine, Japan. The focus of his present work is on Hepatitis C Virus. A/Prof Shoji obtained his PhD from Kyoto University Graduate School of Medicine, Japan in 1997 and was a Visiting Researcher at the National Institute of Infectious Disease, Tokyo, Japan until 1998. From 1998 to 2002, A/Prof Shoji did his Research Fellowship at Harvard Medical School, Boston, US. In 2002, A/Prof Shoji appointed the Chief of Laboratory III, Department of Virology II, National Institute of Infectious Diseases, Tokyo, Japan. A/Prof Shoji received APASL Young Investigator Award in 2007.