Molecular details of regulating the hepatitis C virus replication identified

Hepatitis C virus (HCV) is the main etiological agent of transfusion-associated and sporadic non-A, non-B hepatitis. About half of all infections lead to chronic form of liver disease with various clinical manifestations of an asymptomatic carrier state to chronic active hepatitis, cirrhosis and hepatocellular carcinoma. The hepatitis C virus is transmitted primarily by the parenteral route or by the use of contaminated blood products (prior to 1991). Through the implementation of diagnostic tests for HCV-contaminated blood products, the incidence of new HCV infections in recent years could be dramatically reduced. HCV still remains a serious medical problem, since more than 170 million people are permanently infected with this virus and are at high risk of severe chronic liver disease such as cirrhosis and hepatocellular carcinoma.

As with many other positive strand RNA viruses in addition to the structural proteins also the non-structural proteins (NS) as well as various cellular components are involved in the assembly of viral particles during the viral life cycle of hepatitis C virus. The non-structural proteins are also involved in the maturation of viral replication complexes. This process must be precisely controlled in order to ensure that functional viral replication complexes are assembled. In this process, the temporal regulation of the viral polyprotein processing often plays a crucial role and is a salient feature of the HCV life cycle. Along this line, efficient NS2-NS3 cleavage is absolutely required for successful HCV genome replication.

The precise characterization of the molecular mechanisms underlying this NS2-NS3 cleavage regulation were the subject of work by researchers led by Prof. Norbert Tautz (Institute of Virology and Cell Biology at the University of Lübeck) from Lübeck, Heidelberg and New Heaven, USA. In this study, new insights were gained on how the regulation of the NS2-NS3 cleavage is achieved at the molecular level and why a complete cleavage is a mandatory requirement for the viral life cycle of HCV. They report their findings in the current issue of *PLoS Pathogens*.

"We show in this study that three conserved amino acids of a hydrophobic NS3 surface area represent an important functional switch in the viral life cycle. On the one hand are these amino acids important for the activation of the NS2 protease by NS3 which leads to the efficient NS2-NS3 cleavage. At the same time is one of these three amino acids a critical factor for the HCV genome replication, as revealed by a detailed characterization of the involvement of these NS3 surface residues with respect to their role in viral RNA replication. "

Surprisingly, further experiments showed that the NS2-NS3 cleavage represents a pivotal requirement for the NS5A hyperphosphorylation. As NS5A phosphorylation is linked to viral RNA replication, this NS5A hyperphosphorylation is an indication of the successful assembly of viral replication complexes.

"Our results are indicating, that an orderly cascade of molecular events must take place for the functional assembly of viral replication complexes to occur" explains Prof. Tautz. "In uncleaved NS2-NS3, the NS3 hydrophobic surface area promotes the NS2 protease stimulation and thus the NS2-NS3 cleavage. After successful NS2-NS3 cleavage this NS3 surface area becomes accessible for the next step in the viral life cycle, the assembly of the functional replicase. In the course of this assembly process can the released NS3 surface area now become engaged in new protein-protein interactions

that effectively promote NS5A hyperphosphorylation, and thus the propagation of the viral RNA genome. These steps are currently being examined in more detail in our group."

Publication Title:

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