News

Newly clarified target may shed light on the anti-viral treatment of hepatitis C

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Viral hepatitis B and C are diseases known as ‘‘silent killers.’’ Compared to other types of viral hepatitis, these types frequently become chronic, and chronic hepatitis tends to progress to liver cirrhosis and hepatocellular carcinoma (HCC). Because the progression lacks symptoms, many patients are diagnosed with these advanced diseases along with viral hepatitis when they receive medical treatment. In particular, hepatitis C is likely to develop into HCC and there is no vaccine to prevent this infection, while hepatitis B can be prevented by vaccination. Thus, developing medical treatment for hepatitis C is crucial. Researchers have investigated hepatitis C to clarify its biological mechanism and to develop new targets for therapy, and one of the pioneers in such hepatitis C investigation is Prof. Kazuhiko Koike (*the University of Tokyo, Japan*).

In collaboration with a research group in Osaka University, Japan, Koike found that a kind of protein known as ‘‘proteasome activator PA28γ’’ is involved in the mechanism of the progression of viral hepatitis C to liver cancer. Their work suggested that this protein binds to hepatitis C virus (HCV) core protein and that this reaction is related to oncogenesis *in vivo*. The researchers hope their results will lead to the development of novel therapies for viral hepatitis C.

The research group focused on the HCV core protein. They previously found that degradation of HCV core protein depended on PA28γ inducing the progression of hepatitis C. To clarify the function of PA28γ *in vivo*, they recently created PA28γ knockout HCV core gene transgenic ($PA28\gamma^{-/-}$CoreTg) mice and analyzed this phenomenon using this animal model. They found that the accumulation of fat (steatosis) in the liver, which is known to be induced by HCV and enhance oncogenesis, was induced in $PA28\gamma^{+/+}$CoreTg mice but not in other genotypes including $PA28\gamma^{-/-}$CoreTg mice. HCC also developed only in $PA28\gamma^{+/+}$CoreTg mice but not in $PA28\gamma^{-/-}$CoreTg mice. Furthermore, analyses of gene expression in these genetically-modified mice showed that the transcription of some genes related to lipid biosynthesis in the liver was up-regulated in $PA28\gamma^{+/+}$CoreTg mice in comparison to $PA28\gamma^{-/-}$CoreTg mice and other genotypes. The molecular mechanism of activation of lipid biosynthesis in $PA28\gamma^{+/+}$CoreTg mice was also found to depend on the existence of PA28γ. Results indicated that the up-regulation of lipid biosynthesis in the liver requires the existence of both HCV core protein and PA28γ and that these phenomena might lead to the pathogenesis of steatosis and the development of HCC. Thus, PA28γ may have a crucial role in the progression of hepatitis C and may represent a strong candidate for development of new anti-viral treatments (*Moriishi K et al. Proc Natl Acad Sci USA, 2007; 104:1661-1666.*).

The number of viral hepatitis patients is increasing worldwide. This situation is particularly severe in eastern Asian countries such as Japan and China. In Japan, approximately 70 to 80% of HCC is caused by hepatitis C, and there may be many HCV carriers who are unaware of their situation, especially among the elderly, because they were injected with shared needles during childhood. According to reports in the forum of prevention and treatment for hepatitis C in China (*November 16, 2007; Beijing, China*), the number of hepatitis C patients in China also rapidly increased in 2007 in addition to the continuous spread of hepatitis B, and concerns are that this trend will continue. Combination therapy with pegylated interferon α and ribavirin has been developed as a therapy for chronic hepatitis C. However, estimates are that approximately 70% of hepatitis C patients in Japan are infected with HCV genotype Ib, which research suggests is refractory to interferon therapy. Bio-science researchers must scientifically elucidate hepatitis C and develop an effective medical treatment for this disease.

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