(Okayama, 3 December) **Research led by Okayama University Graduate School of Medicine identifies the signalling pathway for hepatitis B virus recognition and suppression, suggesting a possible anti-viral strategy for the disease.**

Approximately 350 million people worldwide are infected with hepatitis B a disease that can be chronic, leading to cirrhosis and cancer of the liver. It is known to avoid immune responses to persistent infections, making it difficult to prevent progression of the disease. Now researchers at Okayama University, National Center for Global Health and Medicine, and Kagoshima University Graduate School of Medical and Dental Sciences have identified an antiviral signalling pathway that suppresses the infectivity of HBV.

Recent work showed that a DNA sensing molecule - cyclic GMP-AMP synthetase (cGAS) - recognises DNA and can trigger an immune response through the adaptor protein, STING. This ‘cGAS-STING’ signalling pathway was found to be fundamental to the recognition of several other viruses including herpes simplex virus type 1 (HSV-1), vaccinia virus (VACV), and human immunodeficiency virus (HIV), but its role in HBV recognition was still unconfirmed.

Noboyuki Kato at the Okayama University and his colleagues used several human cell lines to test for immune responses to different DNA derived molecules. They found immune responses

to the DNA analogue p-dGdC were only present in the two cell lines that highly expressed cGAS. When cGAS expression was knocked down in these cell types, p-dGdC no longer activated an immune response.

The researchers also demonstrated reduced HBV infectivity in cells with the cGAS/STING pathway compared to controls. “We conclude that the cGAS-STING signalling pathway is required for not only the innate immune response against HBV but also the suppression of HBV assembly,” they conclude in their report. “The cGAS-STING signalling pathway may thus be a novel target for anti-HBV strategies.”

Background

Hbv, hcv and hepatic viruses

Hepatitis is a disease caused by inflammatory cells in the liver. Symptoms include jaundice, low appetite and malaise. The condition can be acute – healing itself over around 6 months – or chronic where it continues to persist. Chronic hepatitis can lead to liver scarring (fibrosis), failure (cirrhosis) and cancer. Causes include certain drugs, most notably alcohol and paracetamol, some plants and organic solvents, other diseases such as autoimmune disease, and most commonly viral infection.

There are five different viruses that lead to hepatitis, described as hepatotropic viruses because they mainly affect the liver. HBV is the most common cause of viral hepatitis, although since most developed countries have adopted routine vaccinations against HBV, hepatitis C caused by hepatitis C virus (HCV) is now the most common in the US. In developing countries HBV infections still reach endemic levels where up to 10% of the population can be infected.

HBV transcription

When HBV infects liver cells it changes from a relaxed circular conformation (rcDNA) to covalently closed circular (cccDNA). Four single-stranded RNAs are transcribed from the cccDNA, including a so-called pregenomic RNA, from which a single-stranded DNA is synthesised through reverse transcription. From this the complementary DNA strand is synthesised to produce the rcDNA.

The researchers found that levels of the pregenomic RNA were reduced in cells expressing the cGAS-STING signalling pathway. It is thought that one of the antibodies triggered by cGAS-STING signalling – ISG56 – binds to the pregenomic RNA structure inhibiting the replication process but the researchers suggest further work is needed.

The conformation of DNA can be right or left-handed. Most DNA *in vitro* or *in vivo* is in the B form which is right-handed. However in certain conditions the B changes to the Z form, which is

left-handed. Antibodies have been found to be Z-form specific suggesting that immune systems recognise the Z form DNA conformation as “non-self”. The results of the researchers analyses also suggest that the HBV virus is Z-form along with other cGAS-STING recognised DNA types including herpes simplex virus type 1 (HSV-1) and double-stranded DNA derived from vaccinia virus (VACV).

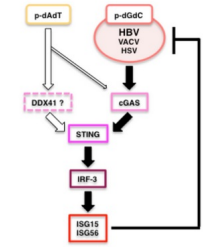


Figure Caption
Proposed models of the cGAS-STING signalling pathways triggered by HBV.

Reference

Hiromichi Dansako, Youki Ueda, Nobuaki Okumura, Shinya Satoh, Masaya Sugiyama, Masashi Mizokami, Masanori Ikeda, Nobuyuki Kato. The cyclic GMP-AMP synthetase-STING signaling pathway is required for both the innate immune response against HBV and the suppression of HBV assembly. *FEBS J*. 2015 Oct 16.

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