Source: Okayama University (Japan), Center for Public Relations and Information Strategy
For immediate release: 03 December 2015

Okayama University research: Cell research shows pathway for suppressing hepatitis B virus

(Okayama, 03 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

Correspondence to
Professor Nobuyuki Kato, Ph.D.
Department of Tumor Virology,
Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, 2-5-1, Shikata-cho, Kita-ku, Okayama 700-8558, Japan.
E-mail: nkato@md.okayama-u.ac.jp
Further information
Okayama University
1-1-1 Tsushima-naka, Kita-ku, Okayama 700-8530, Japan
Public Relations and Information Strategy
E-mail: www-adm@adm.okayama-u.ac.jp
Website: http://www.okayama-u.ac.jp/index_e.html
Okayama Univ. e-Bulletin: http://www.okayama-u.ac.jp/user/kouhou/ebulletin/
About Okayama University (You Tube):
https://www.youtube.com/watch?v=iDL1coqPRYI
Okayama University Image Movie (You Tube):
https://www.youtube.com/watch?v=_WnbJVk2elA
https://www.youtube.com/watch?v=KU3hOIIXS5kk

Okayama University Medical Research Updates (OU-MRU)
Vol.1: Innovative non-invasive 'liquid biopsy' method to capture circulating tumor cells from blood samples for genetic testing
Vol.2: Ensuring a cool recovery from cardiac arrest
Vol.3: Organ regeneration research leaps forward
Vol.4: Cardiac mechanosensitive integrator
Vol.5: Cell injections get to the heart of congenital defects
Vol.6: Fourth key molecule identified in bone development
Vol.7: Anticancer virus solution provides an alternative to surgery
Vol.8: Light-responsive dye stimulates sight in genetically blind patients
Vol.9: Diabetes drug helps towards immunity against cancer
Vol.10: Enzyme-inhibitors treat drug-resistant epilepsy
Vol.11: Compound-protein combination shows promise for arthritis treatment
Vol.12: Molecular features of the circadian clock system in fruit flies
Vol.13: Peptide directs artificial tissue growth
Vol.14: Simplified boron compound may treat brain tumours
Vol.15: Metamaterial absorbers for infrared inspection technologies
Vol.16: Epigenetics research traces how crickets restore lost limbs
About Okayama University

Okayama University is one of the largest comprehensive universities in Japan with roots going back to the Medical Training Place sponsored by the Lord of Okayama and established in 1870. Now with 1,300 faculty and 14,000 students, the University offers courses in specialties ranging from medicine and pharmacy to humanities and physical sciences. Okayama University is located in the heart of Japan approximately 3 hours west of Tokyo by Shinkansen.