David Todd Distinguished Lecture -
Understanding of an Ancient Virus in the Modern Era

Biography

Professor Man-Fung YUEN is currently the Chair Professor of The University of Hong Kong and Li Shu Fan Medical Foundation Professor in Medicine, and the Chief of the Division of Gastroenterology and Hepatology, Queen Mary Hospital, Hong Kong. He obtained his first bachelor's degree of medicine in 1992. His academic accolade is recognized by the achievement of obtaining three doctoral degrees, namely Doctor of Medicine with Sir Patrick Manson Gold Medal in 2001, Doctor of Philosophy in 2005 and Doctor of Science in 2017.

In addition to his innumerable researcher initiated studies over the past 30 years, he has been conducting more than 80 hepatitis B drug related clinical trials so far being recorded in the HKU clinical trial centre. He has already published more than 580 papers in world-renowned medical journals including New England Journal of Medicine, Lancet, Nature Medicine, Lancet Infectious Diseases and Lancet Oncology. To date, he is one of the most influential researchers in the field of hepatitis B in the world. According to the Expertscape academic online platform which analysed 25,130 publications during the period between 2013 and 2023, he is ranked the top 1 researcher under the category of "hepatitis B". Under a broader medical research field, according to another academic performance platform, the AD Scientific Index 2024, he is ranked the 16th world scientist in the field of Gastroenterology and the 1,178th out of 148,666 researchers in all subjects of Medical and Health Sciences. Along with his outstanding research output and leadership in the field, he has been invited to deliver more than 340 lectures all over the world.

Abstract

Although hepatitis B virus (HBV) was discovered in 1967, its presence can be traced back to 7,000 years ago. It is a small DNA virus of approximately 3.2 kilobase in length arranged as a relaxed circular double stranded DNA with the virion size of 42 nm in diameter. Once humans are infected with HBV during early phase of life, the chance of disease chronicity is as high as 90%. In established chronic infection, liver cirrhosis and hepatocellular carcinoma (HCC) are the most devastating outcomes which usually occur after fifth decades of life.

Chronic HBV infection typically undergoes 4-5 disease phases in the life time of infected individuals. Previously, seroconversion from hepatitis B e antigen (HBeAg) to antibody to HBeAg (anti-HBe) was considered as a "healthy" carrier status. However, increasing evidence has proven that this HBeAg seroconversion only represents a transition of high viraemic state to a relatively lower viraemic state. Nevertheless, the risk of development of complications is more dependent on the long duration of persistent "residual" viraemia and other genetic and basal characteristics. The current treatment targeting the lowest viraemic state is capable of reducing the disease complication rate, although it should be taken as life-long viral suppressive therapy.

Along with the revelation of HBV virology including the roles of the chemically inert virus template for replication (the closed covalently circular [ccc] DNA), the integration of HBV DNA into the host genome with an oncogenic driving property and different viral serological markers, disease monitoring and treatment paradigm have changed over the last 10 – 15 years. Occult HBV infection has been increasingly diagnosed with the development of more sensitive assays. The importance of this previously neglected entity is becoming increasingly recognized in the setting of HBV reactivation in patients receiving immunosuppressive therapies and as a cause of previously mislabeled "cryptogenic" HCC.

HBsAg seroclearance (functional cure) is now the advanced goal of treatment of HBV which is associated with a further reduced risk of HCC and with a possibility of stopping life-long treatment of HBV. In the past 10 years, research on novel antiviral therapies has been undergoing with an ever-accelerating pace. These agents target every single step of the HBV replication cycle. Once a functional cure is achieved, the HBV would be adequately controlled by the reawakened immune system (which would have been suppressed by the high load of HBsAg in the body), and as a result, long-term medications can be safely stopped with the achievement of low rate of development of disease complications.

Finally, research on epigenetic and genetic modifications of the HBV genome including integrated HBV DNA are actively underway. Whether these treatments can achieve complete cure (eradication of cccDNA) and/ or sterilizing cure (removal of integrated HBV DNA) of hepatitis B infection remain to be determined.