Evolution in Our Understanding of Hepatitis B Virus Virology and Immunology

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KEYWORDS

• Hepatitis B virus • Pathogenesis • Translational hepatology • cccDNA
• Immunobiology • Immunotherapy • B and T cell responses to HBV
• Therapeutic vaccination

KEY POINTS

- Improvements of our understanding of hepatitis B virus (HBV) virology and immunology have been the foundation for the HBV vaccine and current therapies.
- Persistence of cccDNA in HBV-infected hepatocytes represents the major hurdle to cure.
- Immune-based strategies show promise for successful elimination of the reservoir of HBV-infected hepatocytes.

INTRODUCTION

In this article, we first review milestones in the discovery of hepatitis B virus (HBV), its viral cycle and how this led to the development of early diagnostic tests, the understanding of HBV natural history, and the development of HBV vaccines and early therapies. For readers interested in learning about even more details, we highly recommend these excellent recent review articles.[1–3] In the second part of the article, we review the history and limitations of current antiviral therapies, and feature open questions and how recent advances in our understanding of HBV virology and cellular immunology allow for novel rational treatment targets.

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IDENTIFICATION OF HEPATITIS B VIRUS

The first descriptions of epidemic jaundice likely owing to viral hepatitis are date back to the times of Hippocrates around 400 BC. In the 19th century, epidemic outbreaks of jaundice several weeks after smallpox vaccination were observed. In seminal work published 1885, Luerman traced the source back to vaccine preparations derived from human "lymph,"[4] suggesting that the epidemic jaundice was caused by an infectious agent, which MacDonald in 1908 proposed to be of viral origin.[5] Further vaccination-associated outbreaks of jaundice occurred during the early part of 20th century, mostly after 1909 and during World War II, associated with the use of hypodermic needles. For example, about 50,000 episodes of jaundice were reported in 1942 among US Army soldiers who received yellow fever vaccine that contained human serum.[6,7] In 1947, MacCallum proposed the term "hepatitis B" for infectious jaundice associated with parenteral transmission route ("serum hepatitis") from "infectious epidemic" hepatitis linked to fecal–oral transmission ("hepatitis A").[8] Subsequent studies conducted in human subjects (often vulnerable populations such as prisoners and mentally handicapped children) showed that hepatitis A and B were likely independent pathogens.[9,10]

The field of viral hepatitis was revolutionized in 1963 by the serendipitous discovery of the HBV surface antigen by Blumberg and Alter. As a geneticist, Baruch Blumberg collected blood samples from different ethnic sources worldwide in an effort to identify polymorphisms involved in certain disease susceptibilities (eg, hemophilia). As Blumberg joined the National Institutes of Health, Harvey Alter was also at the National Institutes of Health studying patients with febrile reactions after blood transfusion, hypothesizing that these reactions may involve antibodies to heterologous serum proteins. Importantly, while performing agar gel immunodiffusion assays with sera from patients with a history of multiple transfusions against samples from Blumberg's collection, Alter identified a reaction against a protein antigen that occurred with high frequency in Australian aborigines. Initially called the 'red antigen' based on its assay appearance, this protein was subsequently named Australia antigen (AuAg).[11] AuAg was subsequently linked to viral hepatitis based on its detection specifically in patients with serum hepatitis.[12–14] These breakthroughs led to the development of diagnostic and screening tests for hepatitis. In 1972, radioimmunoassays replaced first generation agar gel immunodiffusion assays in AuAg detection and contributed to a large reduction in transfusion-associated hepatitis in the 1970s.[2]

However, it was initially difficult to determine if AuAg was the pathogen, a part of the pathogen, or a host protein responding to the pathogen in the absence of established cell culture or animal models that could propagate AuAg. Initial electron microscopy analysis of purified AuAg by Blumberg and colleagues[15] identified small round particles of variable size (15–25 nm) that seemed different from known viruses and did not seem to contain nucleic acids by the experimental approaches used then. These observations even led to the speculation that AuAg might be a prionlike agent. However, subsequent electron microscopy studies of AuAg immunocomplexes by David S. Dane showed that AuAg was also incorporated into larger particles with an inner core structure.[16] Recognition of isolated core protein (HBcAg) by patient antibodies[17] suggested that the Dane particles represented the actual HBV, the AuAg being its surface protein (HBsAg). DNA polymerase activity and double-stranded DNA molecules in purified AuAg preparations then showed that the Dane particles contained intact HBV with a nucleic acid genome.[18,19] The HBV DNA was subsequently cloned and elicited acute HBV infection after injection into chimpanzee livers,[20] demonstrating that the Dane particles indeed represented infectious HBV.

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