

Hepadnaviruses - Hepatitis B

“Hepatitis B is a retrovirus with a bad sense of timing” - Don Ganem

Reading: Schaechter's Mechanisms of Microbial Disease, Fourth Edition, Chapter 43 (pp. 426-432).

I. Relevance

- A. 250 million people infected worldwide.
- B. In areas of Africa and East Asia, 50% of the population may be seropositive, 5-15% may be chronically infected (carriers).
- C. Carriers are 200x more likely than non-carriers to develop primary hepatocellular carcinoma.
- D. 300,000 cases per year in the US; 4,000 fatalities.
- E. 70-90% of maternal-neonatal infections result in chronic infection.

II. Key features of Hepatitis B virus

- A. Enveloped virion containing partial double-stranded circular DNA genome
- B. Replication occurs through an RNA intermediate
- C. Virus encodes and carries a reverse transcriptase
- D. Virus encoded several antigenically and clinically predictive important proteins
- E. Virus has a strict tissue tropism to the liver
- F. Virus infected cells produce and release large amounts of HBsAg particles lacking DNA
- G. Viral DNA can integrate into the host chromosome

III. Virion structure

- A. Mature virion (Dane particle)
 - 1. 42 nM in diameter
 - 2. Double shell
 - 3. Outer shell is lipid and surface antigen (HBsAg), a glycoprotein
 - 4. Inner shell is the core, made from core antigen (HBcAg)
 - 5. Within core is a 3.2 kb circular, partially double-stranded DNA, and reverse transcriptase (RT).
- B. Incomplete virus
 - 1. Accumulates in blood of infected individuals in much higher numbers than mature virions.
 - a. Mature virions = $10^5 - 10^7$ per ml
 - b. Incomplete virions = 10^{13} per ml
 - c. Might influence immune response (chaff)
 - 2. Made from HbsAg
 - 3. 22 nM diameter spheres or filaments

IV. Genome structure and organization

- A. 3.2 kb circular, partially double-stranded DNA
 - 1. One strand nicked
 - 2. One strand incomplete
 - 3. Circle is not covalent; base pairing keeps it together
- B. Four genes
 - 1. S encodes surface antigen, HBsAg, outer shell
 - 2. C encodes core antigen, HBcAg, inner shell
 - A. HBeAg is a variant of the C gene product caused by different in-frame translation of a related mRNA.
 - 3. P encodes reverse transcriptase (RT), also sometimes called polymerase
 - 4. X encodes a regulatory protein
 - 5. All encoded on one strand of the DNA
 - 6. Economical: each gene overlaps at least one other

V. Replication cycle

- A. Attachment of specific (unidentified) hepatocyte receptor via HbsAg
- B. DNA lands in nucleus as covalently closed circle
 - 1. Transport mechanism unclear
 - 2. Enzyme(s) that convert the genome to covalently closed circle unknown; could be cellular and/or viral (RT)
- C. DNA transcribed by cellular RNA polymerase II in the nucleus.
 - 1. Full length RNA serves as both genomic RNA and mRNA for HBcAg and reverse transcriptase.
 - 2. Smaller, subgenomic RNA serves as mRNA for HBsAg.
- D. Genomic RNA plus reverse transcriptase are encapsidated with HBcAg in cytoplasm
- E. Reverse transcriptase converts genomic RNA into circular, partially double stranded DNA to complete the core particle
- F. Core particle is further encapsidated with HBsAg via interaction with intracellular membranes.
- G. Virus (mysteriously) exits without killing cell

VI. Pathogenesis

- A. Parenteral, sexual, perinatal
- B. Highly species and tissue specific
- C. Low cytotoxicity; liver pathology results primarily from immune response to virus infection
- D. Acute infection
 - 1. 25% of infected adults develop clinical disease
 - 2. 90% of clinical cases are completely resolved

E. Chronic infection

1. 10% of acute infections result in chronic infection
2. Chronically infected individuals produce infectious virus: carriers
3. Chronic infection may spontaneously resolve, persist in an asymptomatic carrier state, or persist in a chronic or intermittent symptomatic carrier state
4. Chronic infection results in a high incidence of cirrhosis and primary hepatocellular carcinoma
5. Perinatal infection results in chronic infection in 80-85% of cases.
 - a. Immune status of host may determine establishment of chronic infection

F. Hepatocellular carcinoma

1. Mechanism not understood, both virus and immune response may contribute
3. Integrated HBV DNA present in many PHCs, but cause and effect not clear

II. Diagnosis

- A. Serology
- B. Persistent presence of HbsAg means you're a carrier
- C. Presence of *antibody* to HbsAg means you had a previous infection and recovered.

Hepatitis Delta Virus

- I. **Hepatitis delta “virus” (viroid) - agent commonly associated with fulminant hepatitis**
 - A. Single stranded, self-complementary RNA, encapsidated in HbsAg
 - B. Small, amorphous particle
 - C. RNA encodes one protein: delta antigen
 - D. Replicates via RNA directed RNA synthesis, catalyzed by host RNA polymerase II
 1. Delta antigen required for replication, role unknown
 - E. Dependent on HBV as a “helper”
 1. HBV provides HbsAg
 - F. May be acquired as co-infection with HBV, or superinfection of HBV infection
 - G. Exacerbates HBV induced disease

- II. **Vaccination for Hepatitis B and Hepatitis D**
 - A. Hepatitis B Immune Globulin (HBIG)
 1. Made from plasma with high anti-HbsAg
 2. Indicated in post-exposure prophylaxis for newborn infants of HBsAg mothers and for persons with accidental percutaneous or permucosal exposure to blood or secretions from individuals who are HBsAg positive
 - B. HBV vaccine from human plasma
 1. 22 nm incomplete particles purified, and “inactivated” from carriers
 2. Safe, effective, expensive
 - C. Recombinant HBV vaccine
 1. HBsAg gene cloned in yeast expression plasmid, expressed in yeast and purified
 2. Safe, effective, not so expensive
 - D. HBV vaccine protects indirectly against HDV

- III. References
 - A. The CDC summary of Hepatitis B and it’s a very good one.
<http://www.cdc.gov/nip/publications/pink/hepb.pdf>
 - B. The CDC Hepatitis (all kinds) WEB site:
<http://www.cdc.gov/ncidod/diseases/hepatitis/>