

## Hepatitis B Virus

CAS No.: none assigned

Known to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)

Also known as HBV

### Carcinogenicity

Hepatitis B virus (HBV) is *known to be a human carcinogen* based on sufficient evidence from studies in humans.

#### Cancer Studies in Humans

Numerous epidemiological cohort and case-control studies conducted in populations differing by race or ethnicity and in various geographic regions have demonstrated that chronic HBV infection causes liver cancer (hepatocellular carcinoma). These studies generally used relatively sensitive and specific serological markers to assess chronic HBV infection. The association between chronic hepatitis B and hepatocellular carcinoma remained strong after adjustment for hepatitis C infection and potential confounding factors such as use of alcohol and tobacco, medical history factors, and dietary exposure to aflatoxin (in areas where aflatoxin contamination of food is common). A meta-analysis of the combined results of 32 studies published between 1993 and 1997 reported a summary odds ratio of 13.7 (95% confidence interval = 12.2 to 15.4) for development of hepatocellular carcinoma among people chronically infected with HBV (as assessed by the presence of HBV surface antigen in the blood) (Donato *et al.* 1998, NTP 2003).

#### Cancer Studies in Experimental Animals

HBV infects a limited range of hosts, primarily humans and great apes (Tennant 2001); therefore, studies in experimental animals are limited. In chimpanzees, HBV infection does not appear to increase the risk of liver cancer (Muchmore *et al.* 1990). In studies with transgenic mice carrying HBV genes, liver cancer developed in some, but not all, strains that produced high levels of viral surface antigen or X protein (described below, under Properties), but not in strains expressing the entire HBV genome (NTP 2003).

#### Studies on Mechanisms of Carcinogenesis

Hepatocellular carcinoma usually emerges after 30 years of chronic HBV infection. During the decades of chronic infection, liver cells undergo many changes as a consequence of ongoing viral replication. Viral DNA becomes integrated into the host cells' DNA through non-homologous recombination, and the presence of these viral DNA sequences may contribute to development of cancer through multiple steps, by any of several mechanisms. Expression of genes that regulate tissue growth may be altered through *cis*-activation. Viral DNA also may be integrated into the growth-regulatory genes themselves, causing mutation. Integration of viral DNA may result in truncation at the 3' end of the gene coding for the middle surface antigen or the X protein, resulting in production of novel proteins capable of *trans*-activation. The majority of HBV-positive hepatocellular carcinomas contain HBV DNA sequences that code for *trans*-activator proteins. Viral integration also may result in general instability of chromosomal DNA. Chromosome allele loss appears to be more frequent in HBV-positive hepatocellular carcinomas than in HBV-negative hepatocellular carcinomas (NTP 2003).

It also has been suggested that some HBV proteins, such as the surface antigens and the X protein, may contribute to tumor formation. In transgenic mice, overproduction of the HBV large surface

antigen leads to persistent inflammation, production of oxygen radicals, and DNA damage. The X protein may activate viral and host-cell promoters and signal transduction pathways, inhibit DNA repair, and affect the cell cycle and apoptosis. High levels of the X protein may transform immortalized mouse fibroblast (3T3) cells (NTP 2003).

### Properties

HBV is an enveloped DNA virus that infects hepatocytes, causing hepatitis B (Blum *et al.* 1983). It is a member of the *Hepadnaviridae* family, which includes the genera *Orthohepadnavirus* (infecting mammals) and *Avihepadnavirus* (infecting birds). The hepadnaviruses have a characteristic partially double-stranded DNA genome, which is held in a circular conformation by a short, cohesive overlap between the 5' ends of the two strands (Ganem and Schneider 2001). The HBV genome codes for seven proteins: viral DNA polymerase, the core protein (HBcAg), the precore protein, the X protein, and three viral envelope (surface antigen) proteins, large (L), middle (M), and small (S) (NTP 2003). The virion has an icosahedral nucleocapsid, composed of core protein enclosing the viral genome. The nucleocapsid is surrounded by an envelope 42 nm in diameter, which contains (in order of decreasing abundance) the L, M, and S proteins. L is thought to specify the virus's host range, by recognizing cell surface receptors, and S is the immunodominant component of the envelope. The functions of the precore and X proteins are unknown. However, it has been proposed that X affects a variety of cell processes, which may in turn significantly affect hepatocyte gene expression, cell survival, and viral replication. The precore protein is cleaved to form a soluble protein (HBeAg), which is secreted from infected cells and may be detected in the blood of infected individuals (Seeger and Mason 2000, Ganem and Schneider 2001).

### Infection, Prevention, and Treatment

HBV infection can cause acute or chronic hepatitis B. Acute hepatitis B is characterized by tissue changes, including hyperplasia, inflammation, and cell death, which appear to result from the host's immune response to HBV antigen (IARC 1994). Chronic hepatitis B, defined as the presence of circulating HBV surface antigen (HBsAg) for over six months, develops in individuals with acute hepatitis B who are not able to clear the virus. The risk of chronic hepatitis B among HBV-infected individuals appears to depend on the status of the immune system at the time of infection and is much higher in HBV-infected infants and children than in HBV-infected adults. About 70% to 90% of infants infected before one year of age develop chronic hepatitis B, whereas the risk of chronic infection among HBV-infected adults is 5% to 10% (IARC 1994, Hollinger and Liang 2001). In chronic hepatitis B, the patient's immune response to HBV results in cycles of cell death and regeneration that may progress to fibrosis of the liver and cirrhosis (replacement of normal liver tissue with bands of fibrous tissue surrounding nodules of regenerating liver tissue) (Hollinger and Liang 2001).

HBV infection can be prevented by screening of the blood supply, reduction of contact with potentially contaminated fluids in health-care settings, and vaccination. The Occupational Safety and Health Administration has established a bloodborne pathogens standard, based on the concept of universal precautions, which requires that body fluids and materials be treated as infectious (OSHA 1992). Recombinant hepatitis B vaccines, which contain HBsAg (produced by genetically engineered yeast cells), have been available in the United States since the 1980s and are recommended for all infants and for individuals at high risk (Hollinger and Liang 2001). Hepatitis B is treated with immunomodulators (drugs that affect the immune system and are not specific for HBV), antiviral drugs, and combination

therapy with both drug types; however, these drugs have limited efficacy (Hollinger and Liang 2001, Schalm *et al.* 2002).

## Detection

HBV infection is confirmed by detection of HBV proteins, antibodies against HBV proteins, or HBV DNA in the blood. The detection of different proteins and antibodies against these proteins are indicators of different stages of infection. The presence of HBsAg indicates acute or chronic HBV infection, whereas the presence of anti-HBsAg antibodies indicates immunity (due to resolved infection or vaccination) (Hollinger and Dienstag 1995). Strictly speaking, chronic HBV infection is defined by detection of serum HBsAg in two tests six months apart; however, this criterion is not practical for most epidemiological studies. Because adults who are not carriers of HBV are highly unlikely to test positive for HBsAg, a single positive test result is considered a valid indicator of chronic carrier state in epidemiological studies. Assays approved by the U.S. Food and Drug Administration include enzyme immunoassays or radioimmunoassays for HBsAg, anti-HBsAg antibody, and anti-HBcAg antibody (FDA 2002).

## Exposure

The major routes of HBV transmission are parenteral (primarily by injection or transfusion), through sexual contact, from mother to infant at the time of birth, and through health-care practices (Hollinger and Liang 2001). In U.S. surveillance studies conducted in 1992–93, most cases resulted from heterosexual transmission (41%), followed by intravenous drug use (15%) and homosexual transmission (9%); however, 31% of HBV infections were not associated with any known risk factors (CDC 2002). The risk of HBV transmission via transfusion in the United States has been estimated at 1 in 63,000 (Glynn *et al.* 2000); donor education, donor screening, and improved laboratory testing procedures have helped to decrease the risk. In areas where HBV infection is endemic, an important route of transmission is from mother to infant.

Worldwide, about two billion people have been infected with HBV, and over 350 million have chronic hepatitis B. The prevalence of chronic infection varies geographically, ranging from low (less than 2%) in Western Europe, Australia, and North America, to intermediate (2% to 7%) in parts of Southern and Eastern Europe, the Middle East, Japan, West Asia through the Indian subcontinent, and parts of Central and South America, to high (8% or more) in Africa, Asia east of the Indian subcontinent, the Pacific Basin, the Amazon Basin, the Arctic rim, the Asian republics previously part of the Soviet Union, and parts of the Middle East (WHO 2000). In the United States, data from the National Health and Nutrition Examination Survey indicate that the prevalence of HBV infection (both chronic and resolved) decreased from 5.5% for 1976 through 1980 to 4.9% for 1988 through 1994 (McQuillan *et al.* 1999).

The incidence of acute HBV is decreasing in the United States, largely as a result of declining incidence among homosexual men and intravenous drug users, screening of blood products, and vaccination; the incidence decreased from 13.8 per 100,000 in 1987 to 3.3 per 100,000 in 1998. In 2000, the incidence of acute hepatitis B was higher in males than females and highest among individuals aged 25 to 39 (Goldstein *et al.* 2002). The Centers for Disease Control and Prevention (CDC) believed the number of reported symptomatic cases to be much smaller than the actual number of new infections. In particular, infections among infants and young children are likely to be underestimated, because most infections in this age group are asymptomatic. CDC estimated that between 1995 and 1999, 105,000 new infections per year occurred in the United States (McQuillan *et al.* 1999).

## Regulations

### Department of Transportation (DOT)

Infectious substances are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

### Food and Drug Administration (FDA)

Regulations have been established to guard against the spread of hepatitis B through donation of blood, serum, and human immune globulin, including requirements for donor screening, product testing, and product labeling.

Each donation of blood, plasma, or serum to be used in preparing a biological product shall be tested for the presence of hepatitis B surface antigen.

21 CFR 1270 and 1271 prescribe procedures, including donor screening and tissue testing, to ensure that tissues intended for human transplant or other human cells, tissues, and cellular and tissue-based products are free of hepatitis B.

### Occupational Safety and Health Administration (OSHA)

Comprehensive regulations have been developed for employers to develop and adhere to exposure control plans for bloodborne pathogens.

An employer shall make the hepatitis B vaccine available to employees who have had exposure to pathogenic microorganisms.

All work-related needlestick injuries and cuts from sharp objects that are contaminated with another person's blood or other potentially infectious material must be recorded.

First-aid training program trainees must have adequate instruction in the value of universal precautions for preventing infectious diseases.

### Public Health Service (PHS)

Regulations have been established to control the spread of hepatitis from hemodialysis treatment.

## References

- Blum HE, Stowring L, Figus A, Montgomery CK, Haase AT, Vyas GN. 1983. Detection of hepatitis B virus DNA in hepatocytes, bile duct epithelium, and vascular elements by *in situ* hybridization. *Proc Natl Acad Sci U S A* 80(21): 6685–6688.
- CDC. 2002. Slide sets associated with NIP's *Epidemiology and Prevention of Vaccine-Preventable Diseases* course, 7th Edition *Pink Book*, Chapter 14: Hepatitis B. Centers for Disease Control and Prevention. Last updated 4/9/02. Last accessed: 12/23/03.
- Donato F, Boffetta P, Puoti M. 1998. A meta-analysis of epidemiological studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma. *Int J Cancer* 75(3): 347–354.
- FDA. 2002. *Licensed/Approved HIV, HTLV and Hepatitis Tests*. U.S. Food and Drug Administration. Last updated: 12/16/03.
- Ganem D, Schneider R. 2001. *Hepadnaviridae: the viruses and their replication*. In *Virology*. Knipe DM, Howley PM, eds. Philadelphia: Lippincott, Williams, and Wilkins. pp. 2923–2969.
- Glynn SA, Kleinman SH, Schreiber GB, Busch MP, Wright DJ, Smith JW, Nass CC, Williams AE. 2000. Trends in incidence and prevalence of major transfusion-transmissible viral infections in US blood donors, 1991 to 1996. *Retrovirus Epidemiology Donor Study (REDS)*. *JAMA* 284(2): 229–235.
- Goldstein ST, Alter MJ, Williams IT, Moyer LA, Judson FN, Mottram K, Fleener M, Ryder PL, Margolis HS. 2002. Incidence and risk factors for acute hepatitis B in the United States, 1982–1998: implications for vaccination programs. *J Infect Dis* 185(6): 713–719.
- Hollinger FB, Dienstag JL. 1995. Hepatitis B and D viruses. In *Manual of Clinical Microbiology*. Murray PR, Baron EJ, eds. Washington, DC: ASM Press. pp. 1033–1049.
- Hollinger FB, Liang TJ. 2001. Hepatitis B virus. In *Fields Virology*. Knipe DM, Howley PM, eds. Philadelphia: Lippincott, Williams and Wilkins. pp. 2971–3036.
- IARC. 1994. Hepatitis B virus. In *Hepatitis Viruses*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 59. Lyon, France: International Agency for Research on Cancer. pp. 45–164.
- McQuillan GM, Coleman PJ, Kruszon-Moran D, Moyer LA, Lambert SB, Margolis HS. 1999. Prevalence of hepatitis B virus infection in the United States: the National Health and Nutrition Examination Surveys, 1976 through 1994. *Am J Public Health* 89(1): 14–18.
- Muchmore E, Socha WW, Krawczynski C. 1990. HCC in chimpanzees. In *Viral Hepatitis and Hepatocellular Carcinoma*. Sung JL, ed. Hong Kong: Excerpta Medica. pp. 698–702.
- NTP. 2003. *Report on Carcinogens Background Document for Hepatitis B Virus*. National Toxicology Program. [http://ntp.niehs.nih.gov/ntp/newhomeroc/roc11/HBV\\_RG2Public.pdf](http://ntp.niehs.nih.gov/ntp/newhomeroc/roc11/HBV_RG2Public.pdf).
- OSHA. 1992. *Bloodborne Pathogens Final Standard*, Fact Sheet No. OSHA 92–46. OSHA Archive. Occupational Safety and Health Administration. [http://www.osha.gov/pls/oshaweb/owadisp.show\\_document?p\\_table=FACT\\_SHEETS&p\\_id=139](http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=FACT_SHEETS&p_id=139).
- Schalm S, De Man R, Janssen H. 2002. Combination and newer therapies for chronic hepatitis B. *J Gastroenterol Hepatol* 17(Suppl 3): S338–S341.
- Seeger C, Mason WS. 2000. Hepatitis B virus biology. *Microbiol Mol Biol Rev* 64(1): 51–68.
- Tennant BC. 2001. Animal models of hepadnavirus-associated hepatocellular carcinoma. *Clin Liver Dis* 5(1): 43–68.
- WHO. 2000. *Hepatitis B*. World Health Organization. Last updated: 10/00. (This version of the WHO Fact Sheet is no longer available on the WHO Web site.)