

Hepatitis B

Virus

supervised by:
Dalia Alsarar

Require for medical Virology course

Accomplished by:

Areeb M. Albarqawi 434925248

Asma A. Aldarwish 434925583

Noura D. Aldahmash 434925248

Afnan A. Alghamdi 434203255

Shorouq M. Almutairi 433203380

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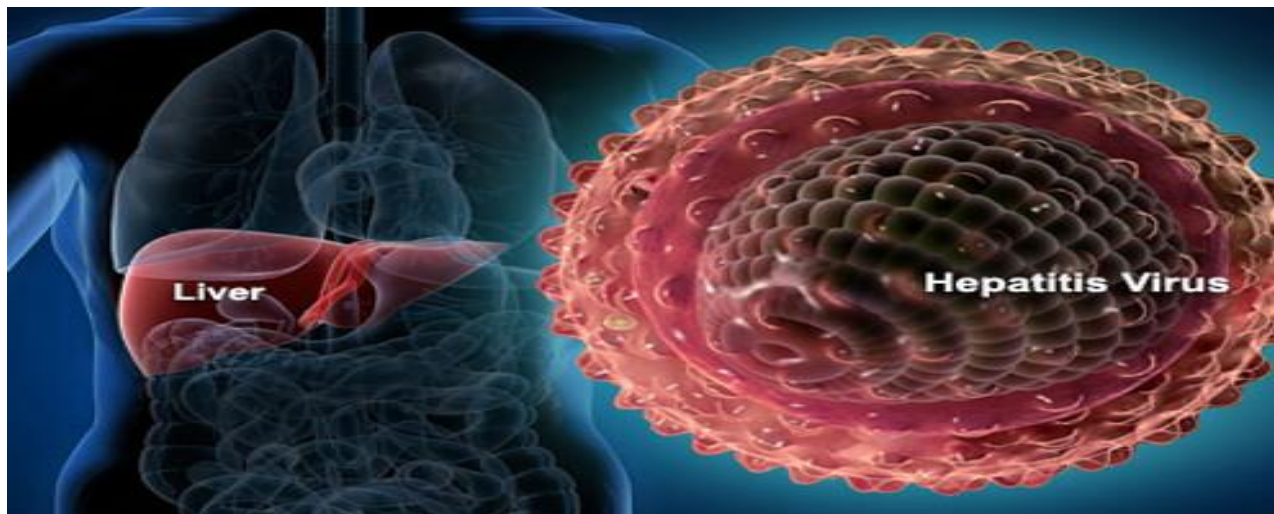
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Introduction:

Hepatitis is an inflammation of the liver. It may be caused by drugs, alcohol use, or certain medical conditions. However, in most cases, a virus causes it. This is known as viral hepatitis, and the most common forms are hepatitis A, B, and C. ⁽¹⁾

Hepatitis B virus (HBV) infection is a major cause of morbidity and mortality worldwide. The World Health Organization (WHO) has estimated that ~2000 million people worldwide have been infected with HBV and that 350 million of these are chronically infected. Of those chronically infected, it is estimated that 65 million will die from liver disease due to their HBV infection. ⁽²⁾

Many adults who get hepatitis B have mild symptoms for a short time and then get better on their own. However, some people are not able to clear the virus from the body, which causes a long-term infection. Nearly 90% of infants who get the virus will carry it for life. Over time, hepatitis B can lead to serious problems, such as liver damage, liver failure, and liver cancer. ⁽¹⁾



- (A) History of the disease.⁽³⁾

- ❖ **8th Century:** Infectious Nature of HBV suggested
- ❖ **17th-19th Centuries:** Outbreaks of epidemics of jaundice in military and civilian populations during wars
- ❖ **1883:** Lurman reports outbreaks of serum hepatitis following vaccination of Dockers
- ❖ **1908:** McDonald postulates that the infectious jaundice is caused by a virus
- ❖ **1939-1945:** WWII-A series of outbreaks after vaccination for measles and yellow fever
- ❖ **1947:** McCullum classifies viral hepatitis into two types-
 - *Viral hepatitis A*---> *Infectious hepatitis*
 - *Viral hepatitis B*---> *Serum hepatitis*

- ❖ **1965:** Blumberg discovers Australia antigen (HBsAg) in aborigines and shows presence of antigen At high frequency in patients with leukemia and children with Down's syndrome
- ❖ **1970:** Dane discovers the Dane particle (complete HBV particle)
- ❖ **1972:** Discovers HBeAg
- ❖ **1973:** Feinstone and Purcell identifies HAV
- ❖ **1977:** Rizzetto describes delta antigen HDV
- ❖ **1983:** Recovery of HEV
- ❖ **1988:** Chiron group (Choo, Kuo, Houghton) clones and identifies HCV.
- ❖ **1995:** Abbot group reports GB Virus-C (GBV-C) and Genelabs group reports in 1996 hepatitis G virus (HGV) ---GBV-C=HGV
- ❖ **1996:** Chang's group at NTUH reports in *JAMA* the successful prevention of HBV infection by Nation-wide vaccination on newborn babies launched in 1984 in Taiwan.
- ❖ **1997:** Chang's group at NTUH reports in *NEJM* a decrease in annual incidence rate of Hepatocellular carcinoma in children ascribed to nation-wide vaccination against HBV on newborn babies launched in 1984 in Taiwan.

-(B) Introduction of the virus:

HBV is a small, double-shelled virus . The virus has a small circular DNA genome that is partially double-stranded. HBV contains numerous antigenic components, including HBsAg, hepatitis B core antigen (HBcAg), and hepatitis B e antigen (HBeAg). Humans are the only known host for HBV, although some nonhuman primates have been infected in laboratory conditions.⁽⁴⁾

A hepatitis B infection can result in either an acute infection or a chronic infection. The risk of developing a chronic hepatitis B infection is directly related to the age at which a person is first exposed to the hepatitis B virus. The younger a person is when they are first infected, the greater the risk of developing a chronic hepatitis B infection

Most pregnant women do not know whether they are infected with hepatitis B and can unknowingly pass the virus to their newborns during childbirth. Therefore, since the risk of newborns becoming chronically infected at birth is so high, both the World Health Organization and the U.S. Centers for Disease Control and Prevention recommend that all infants receive the first dose of the hepatitis B vaccine within 12-24 hours after birth.⁽⁵⁾

➤ Chronic Hepatitis B Infection :

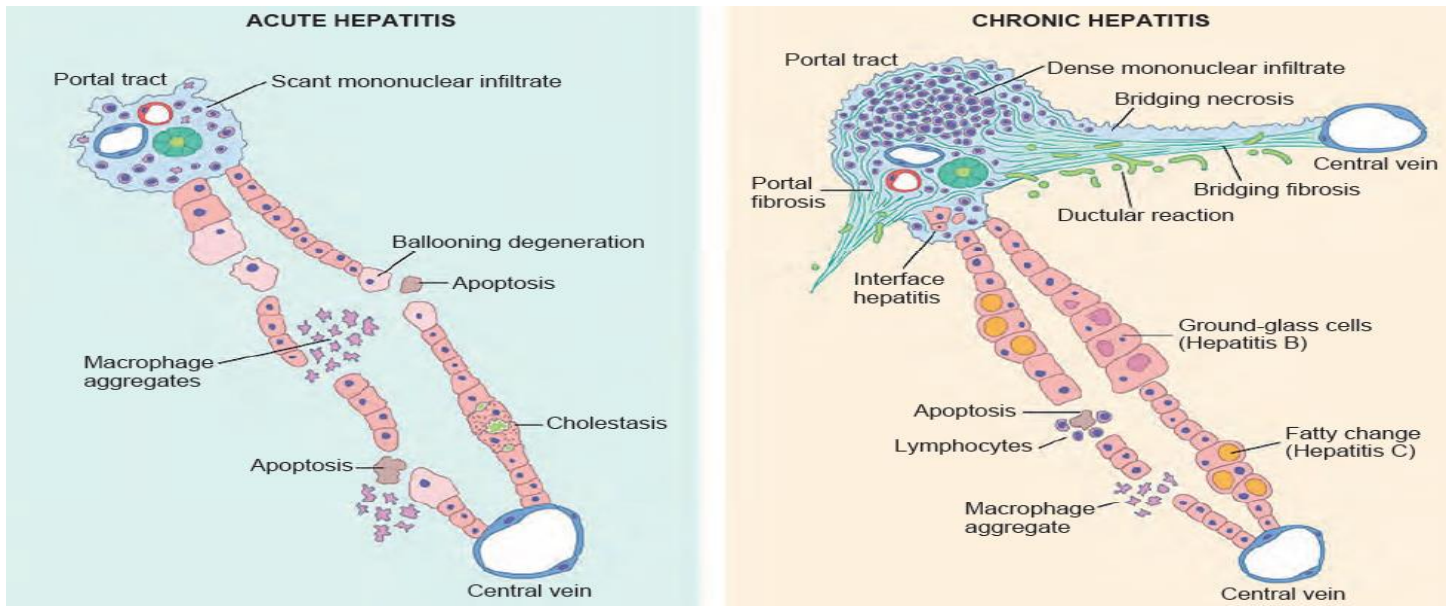
When you are infected as newborns or young children, your immature immune systems don't notice or fight the virus and it travels to your liver and begins reproducing., a hepatitis B infection can continue for years. When the infection lasts longer than six months, it is considered a chronic or long-term infection..⁽⁶⁾

➤ Acute Hepatitis B Infection:

When you are infected with HBV as healthy adults, about 90 percent of you are able to get rid of the infection within six months. It's take 6 noths for your immune systems to generate antibodies and eradicate the infection in your liver. This short-term infection is called acute hepatitis b.

How to know if you have an Acute or Chronic HBV?

To determine if you have an acute or chronic infection, you must be tested for hepatitis B over a six-month period. The specific test that indicates if you are infected is the hepatitis B surface antigen (HBsAg) test. This antigen covers the surface of the virus and usually there are lots of HBsAg in your blood when you're infected. If you test positive for HBsAg for longer than six months, it means you have a chronic hepatitis B infection..⁽⁶⁾



-(C) The distribution of the virus :

Hepatitis B prevalence is highest in sub-Saharan Africa and East Asia, where between 5–10% of the adult population is chronically infected. High rates of chronic infections are also found in the Amazon and the southern parts of eastern and central Europe. In the Middle East and the Indian subcontinent, an estimated 2–5% of the general population is chronically infected. Less than 1% of the population in Western Europe and North America is chronically infected. (7)

-(D) Epidemiology : (8)

The prevalence of chronic HBV infection varies greatly in different part of the world . The prevalence of chronic HBV infection worldwide could be categorized as high, intermediate and low endemicity. The age at the time of infection is associated with the endemicity of HBV infection .

High Endemicity:

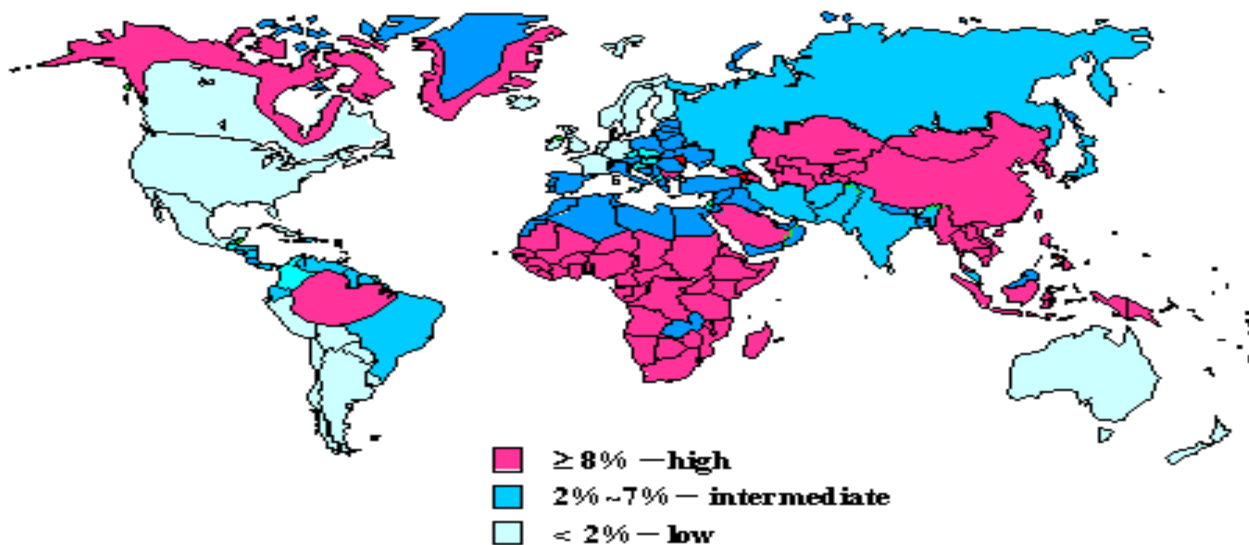
The prevalence of HBV infection varies markedly throughout regions of the world . Hepatitis B is highly endemic in developing regions with large population such as South East Asia, China, sub-Saharan Africa and the Amazon Basin, where at least 8% of the population are HBV chronic carrier. In these areas, 70–95% of the population shows past or present serological evidence of HBV infection. Most infections occur during infancy or childhood. Since most infections in children are asymptomatic, there is little evidence of acute disease related to HBV , but the rates of chronic liver disease and liver cancer in adults are high .

Intermediate Endemicity:

Hepatitis B is moderately endemic in part of Eastern and Southern Europe, the Middle East, Japan, and part of South America. Between 10–60% of the population have evidence of infection, and 2-7% are chronic carriers. Acute disease related to HBV is common in these areas because many infections occur in adolescents and adults; however, the high rates of chronic infection are maintained mostly by infections occurring in infants and children. In these areas, mixed patterns of transmission exist, including infant, early childhood and adult transmission.

Low Endemicity:

The endemicity of HBV is low in most developed areas, such as North America, Northern and Western Europe and Australia. In these regions, HBV infects 5–7% of the population, and only 0.5–2% of the population are chronic carriers. In these areas, most HBV infections occur in adolescents and young adults in relatively well-defined high-risk groups, including injection drug user, homosexual males, health care workers, patients who require regular blood transfusion or hemodialysis.



Classification of hepatitis B:⁽⁹⁾

Order	Unassigned
Family	<i>hepadnaviridae</i>
Genus	<i>Orthohepadnavirus</i>

Structure and Genome of hepatitis B:⁽¹⁰⁾

The HBV virion, historically referred to as the “Dane particle,” consists of an icosahedral nucleocapsid enclosed in an envelope.

The short HBV DNA genome is unusual in that it is a partly single-stranded, partly double-stranded, noncovalently closed, circular DNA molecule (that is one strand is longer than the other) as shown in figure. The short “plus” strand which can vary in length, is only 50 to 80 percent as long as its complementary strand, the “minus” strand. The circular structure of the genome is maintained by base-pairing the strands at one end.

Proteins (Virulence Factors):

Structural proteins and their function:⁽¹¹⁾

1. Hepatitis B Surface antigen (HBsAg)

There are three different types of hepatitis B surface antigens; small hepatitis B surface antigen (HBsAg or SHBsAg), middle hepatitis B surface antigen (MHBsAg), and large hepatitis B surface Antigen (LHBsAg). HBsAg is the smallest protein of the hepatitis B surface proteins and has historically been known as the Australia antigen (Au antigen). It is very hydrophobic, containing four-transmembrane spanning regions. This protein is the prime constituent of all hepatitis b particle forms and appears to be manufactured by the virus in high quantities. It also contains a highly antigenic epitope which may be responsible for triggering immune response. Regardless of the high antigenicity and prevalence of these particles, the immune system appears basically oblivious to their presence. Reduced production of HBsAg leads to intracellular retention of the virus. MHBsAg contains an additional amino-acid domain and appears to reside extracellularly. Although some believe that the MHBsAg is responsible for HBV attachment, MHBsAg is not required for HBV infectivity and therefore it is more likely that it contributes to viral attachment as a secondary mechanism. LHBsAg is the largest of the HBV surface proteins, containing three domains within the HBV encoding region. HBV is believed to be involved in liver attachment due to its variability among patients. It is also believed to be responsible for mediating viral attachment into host cells, although this has yet to be confirmed experimentally.

2) Hepatitis B Core Antigen (HBcAg):

The only HBV antigen that can not be detected directly by blood test, this antigen can only be isolated by analyzing an infected hepatocyte. A 185 amino acid protein is expressed in the cytoplasm of infected cells, they are highly associated with nucleocapsid assembly.

3) Hepatitis B e Antigen (HBeAg):

The e antigen is named due to its "early" appearance during an acute HBV infection. Thought to be located in the core structure of the virus molecule, this antigen can be detected by blood test. If found its usually indicative of complete virus particles in circulation.

Non-Structural proteins: ⁽¹²⁾

1. **A nonstructural regulatory protein designated the "X" protein:**

a key regulatory protein of the virus that is at the intersection of HBV infection, replication, pathogenesis, and possibly carcinogenesis. The exact role of HBx in viral replication has yet to be established, and its link to the progression of HCC (hepatocellular carcinoma [HCC]) remains controversial. Moreover, it is still unclear whether development of HCC associated with chronic infection by HBV involves a viral protein, is solely the consequence of a continual inflammatory response to infection, or requires both. Understanding the role of HBx in HBV replication and its effect on hepatocyte biology may help resolve this issue.

Transmission of hepatitis B:

Hepatitis B is found in blood and in body fluids, including semen and vaginal fluids. Even though studies have shown minute quantities of the virus can be present in saliva, tears and breast milk, they are not considered to be in high enough levels to transmit the virus.

The most common ways hepatitis B is spread include:

- sexual contact
- sharing of injecting equipment
- needle stick injuries in a health care setting
- reuse of unsterilized or inadequately sterilized needles
- child-to-child transmission through contact such as biting
- sharing personal items such as razors, toothbrushes, or hair and nail clippers
- mother-to-baby.

Hepatitis B is NOT spread by contaminated food or water, and cannot be spread through casual or social contact such as kissing, sneezing or coughing, hugging, or eating food prepared by a person with hepatitis B.⁽¹³⁾



Penetration and the target organ:⁽¹⁴⁾

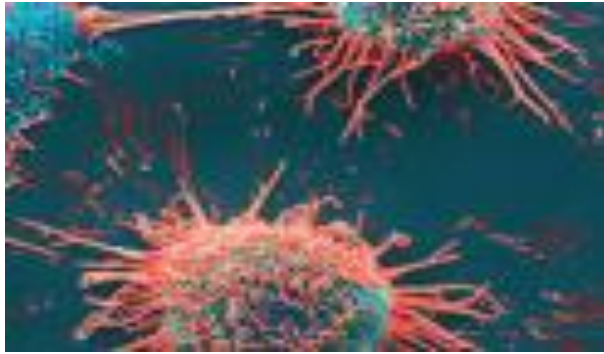
Hepatitis B is a viral infection that attacks the liver and can cause both acute and chronic disease.

The liver plays an essential role in energy storage and conversion, blood homeostasis, chemical detoxification, and immunity to microbial infections. Although the liver is composed of many different types of cells, much of the functional activity resides in hepatocytes (which constitute 70% of the liver), bile ductile epithelium, and Kupffer cells (macrophages) Among these, hepatocytes and bile ductile epithelial cells are unique to the liver and are also closely related. In fact, they may originate during embryonic life from a common and also may be replaced by proliferation and differentiation of a common progenitor cell in response to very acute forms of liver injury (Bill & Melinda , 2014).

Because hepatocytes are the major cell type in the liver, it might be expected that they would also be the major target of infection by a liver-tropic virus such as HBV. Indeed, this appears to be the case. Hepatocytes are the only confirmed site of replication for all members of this virus family. Bile ductile epithelial cells may also be a target of infection, as may a subset of cells in the pancreas, kidneys, and lymphoid system. However, the evidence for replication of the orthohepadnaviruses in bile ductless and at extra hepatic sites is in some cases controversial or incomplete, and these sites are not usually considered in discussions of viral reproduction and pathogenesis. This approach to infections is at least compatible with the notion that many of the extra hepatic symptoms of infection that are not attributed to liver dysfunction are the result of deposition of antibody-antigen complexes. Thus, for the purpose of simplicity, we discuss infection only in the context of hepatic manifestations. The implications of extra hepatic infections have yet to be determined.

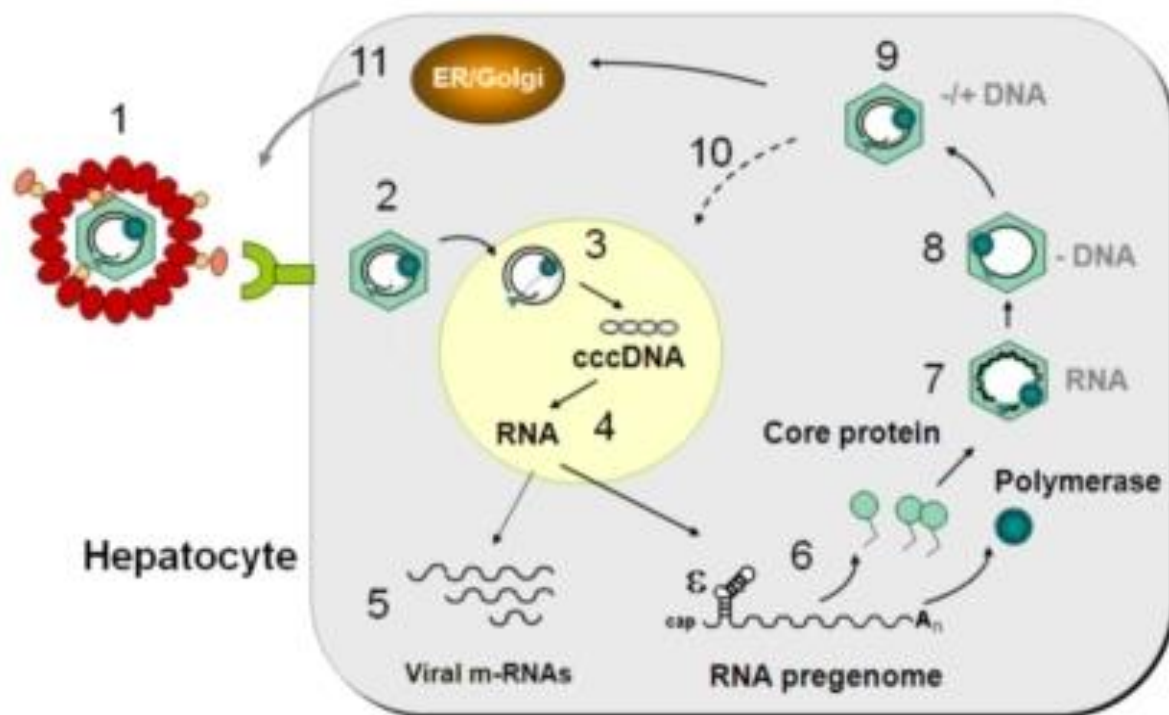
The liver itself is usually considered, for convenience, to be divided into small compartments called lobules. This subdivision emphasizes the role of the liver in relation to blood flow. While this view of liver anatomy is somewhat arbitrary, it provides a convenient way of considering liver function, development, regeneration, and pathogenesis. An essentially one-dimensional view of a section of a **“classical” lobule is illustrated in Fig (Bill & Melinda , 2014).**

In this view, blood enters the lobule through portal veins and hepatic arteries and is distributed by smaller vessels to enter the sinusoidal spaces, created by plates of hepatocytes. The plates are generally one hepatocyte thick in mammals and two hepatocytes thick in birds. Blood passes through these spaces, which are lined by fenestrated endothelial cells and fixed macrophages (Kupffer cells), where the various functional interactions take place. The blood is then collected in central veins and exits the liver. (It should be noted that because of the rather homogeneous nature of liver anatomy, blood from each portal vein and artery will flow to several surrounding central veins; a more thorough discussion of liver structure and function is presented in reference. Generally, the distance from a portal vein to a central vein is 20 to 30 hepatocytes. During catabolism of heme produced by red blood cell breakdown in the liver, bile is formed and secreted into bile canaliculi, small channels formed at the junctions of hepatocytes. Bile flows in the opposite direction from blood, passing through a region known as the canal of Hering to enter bile ducts. From there, it flows into larger ducts and is eventually transported to the gallbladder and intestine (Bill & Melinda , 2014). (14)



Replication Cycle (the main site):

hepatitis B virus has a high degree of species and tissue specificity that results in very high levels of viral replication. HBV uses reverse transcription to copy its DNA genome in several steps ..



(15)

Attachment:⁽¹⁶⁻¹⁷⁾

The first phase of the viral (HBV) replication cycle, begins with the attachment of virus to the host cell , by binding to a receptor on the surface of the cell .

1) Penetration

The HBV penetration the cytoplasm as "a core section" which is contain the (viral DNA and DNA Polymers) . The core moves to nuclear of the cell , as it travels through the cytoplasm , the core begins to disintegrate releasing the viral DNA and DNA Polymers which then pass to the nuclear pore and then to nucleus .

2) Uncoating

At this point the viral DNA exists as a partially double-stranded circular form , the host cell enzymes they named in several steps including completion of the positive strand of DNA and covalent of the circle to form highly stable covalently closed circular DNA known as (cccDNA)

3) Replication

During the course of the viral lifecycle more copies of cccDNA buildup in the nucleus forming a stable reservoir a viral genetic material within the settle , this cccDNA functions as a minichromosome within the nucleus serving as a tamplate for cellular enzymes to produce new viral pre genomic and subgenomic mRNA . the viral RNA molecules passed through the nuclear pores to enter the cell cytoplasm hear some of the mRNA is translated by the cellular ribosomes to produce HBV core proteins .

viral polymerase has three functional activities :

-Priming initiates the process of negative strand DNA synthesis .

-reverse transcription the negative strand of DNA is generated by reverse transcription with degradation of pre genomic RNA .

-DNA synthesis the negative strand DNA then acts as a template for synthesis of a positive strand DNA with variable length.

the principal function of the polymerase is to convert pre genomic viral RNA into viral DNA for **incorporation into the next generation of hepatitis B Varian's** .

Assembly and Egression:⁽¹⁸⁾

Assembly's HBV-Cure research team is discovering and developing multiple drug candidates that address both upstream and downstream targets in the HBV lifecycle for possible use in combination therapy. The goal is an orally-administered regimen that eradicates the HBV infection, unlike current therapies that only keep the virus in check. Assembly has built a senior scientific team with decades of combined experience working on HBV.

In the vision assembly, the nucleocapsid reach the ER where they associate with the envelope proteins and bud into the lumen of the ER from which they are associated via the Golgi apparatus out of the cell.

The new, mature viral nucleocapsid can then follow two different intracellular pathways. One of which leads to formation and secretion of new visions whereas the other leads to amplification of viral

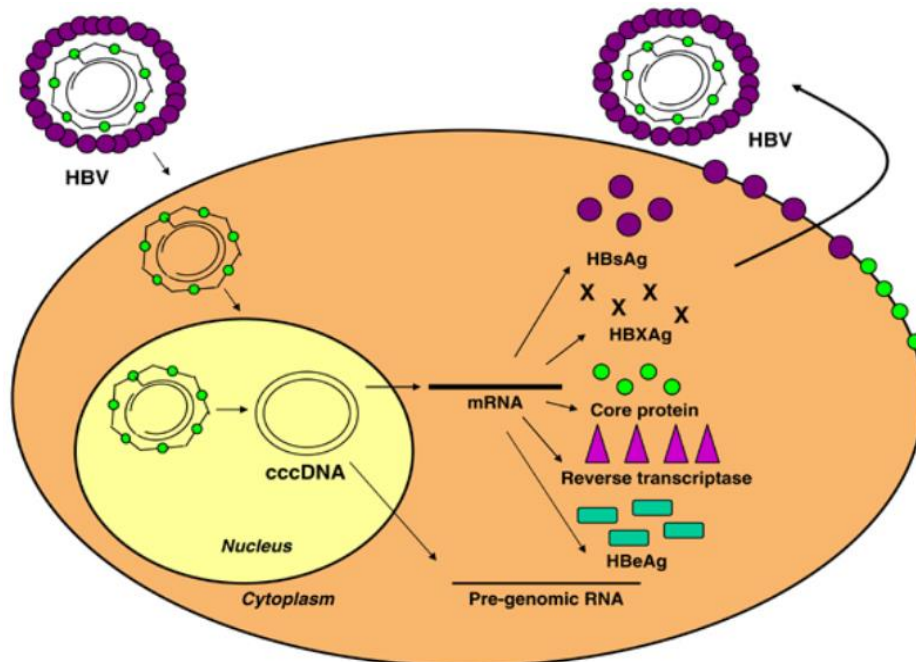
genome inside nucleus. The pre-core polypeptide is transported into the ER lumen where it's amino and carboxyl terminal is trimmed and the resultant protein is secreted as procure antigen.

The X protein contributes to the efficiency of HBV replication by integrating with different transcription factors and is capable of stimulating both cell proliferation and cell death.

The HBV polymerase is multifunctional enzyme. The products of P gene are

involved in multiple function of the viral life cycle, including priming activity to initiate ,minus-strand DNA synthesis a polymerase activity which synthesis DNA by using either RNA or DNA templates, a nuclease activity which degrades the RNA strand of RNA-DNA hybrids, and the packaging of the RNA praenomen into nucleocapsids. . Nuclear localisation signals on the polymerase mediate the transport of covalently linked viral genome through the nuclear pore

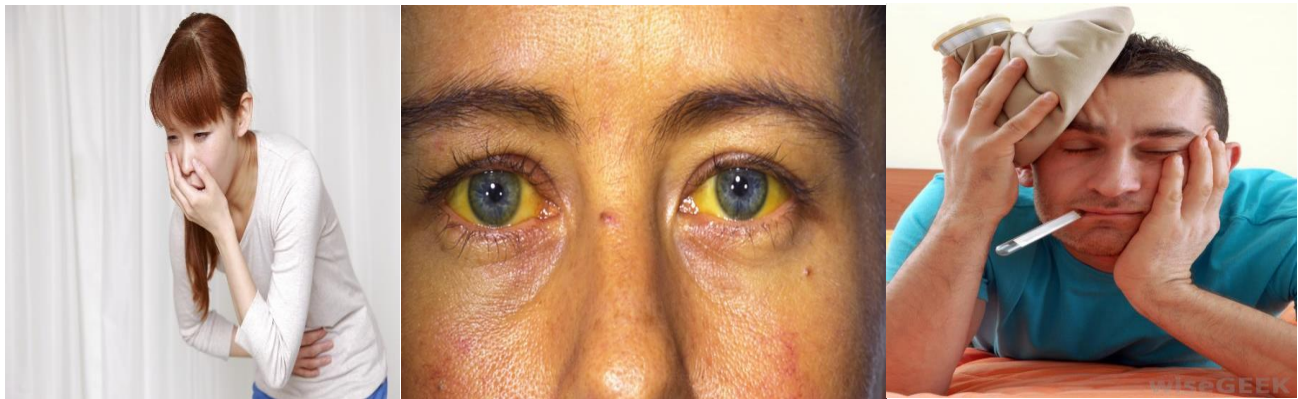
The 3.5 kb species, spanning the entire genome and termed pregenomic RNA, is packaged together with HBV polymerase and a protein kinase into core particles where it serves as a template for reverse transcription of negative strand DNA .the RNA to DNA conversion takes place inside the particles Ebression/budding out14 Three independent reports have demonstrated that HBV budding and egress depend on functions of the so-called multivesicular body (MVB) pathway .MVBs have the unique ability to generate intraluminal vesicles (ILV) that bud away from the cytosol, a process topologically equivalent to that of enveloped virus budding. Normally, cargo destined for either degradation, lysosomal functions, or exosomal release are sequestered (hidden) into these inwardly budding vesicles. The MVBs then fuse with the lysosome or the plasma membrane for ILV delivery.



Symptoms:^(19 – 20)

Many people with hepatitis B infection don't know they have it, because they don't have symptoms. But if you do have symptoms, they may include:

- Feeling very tired.
- Mild fever.
- Headache.
- Not wanting to eat.
- Feeling sick to your stomach or vomiting.
- Belly pain.
- Tan-colored bowel movements (stools).
- Dark urine.
- Yellowish eyes and skin (jaundice). Jaundice usually appears only after other symptoms have started to go away.



Diagnosis and Cytopathic effect:

Diagnosis:⁽²¹⁾

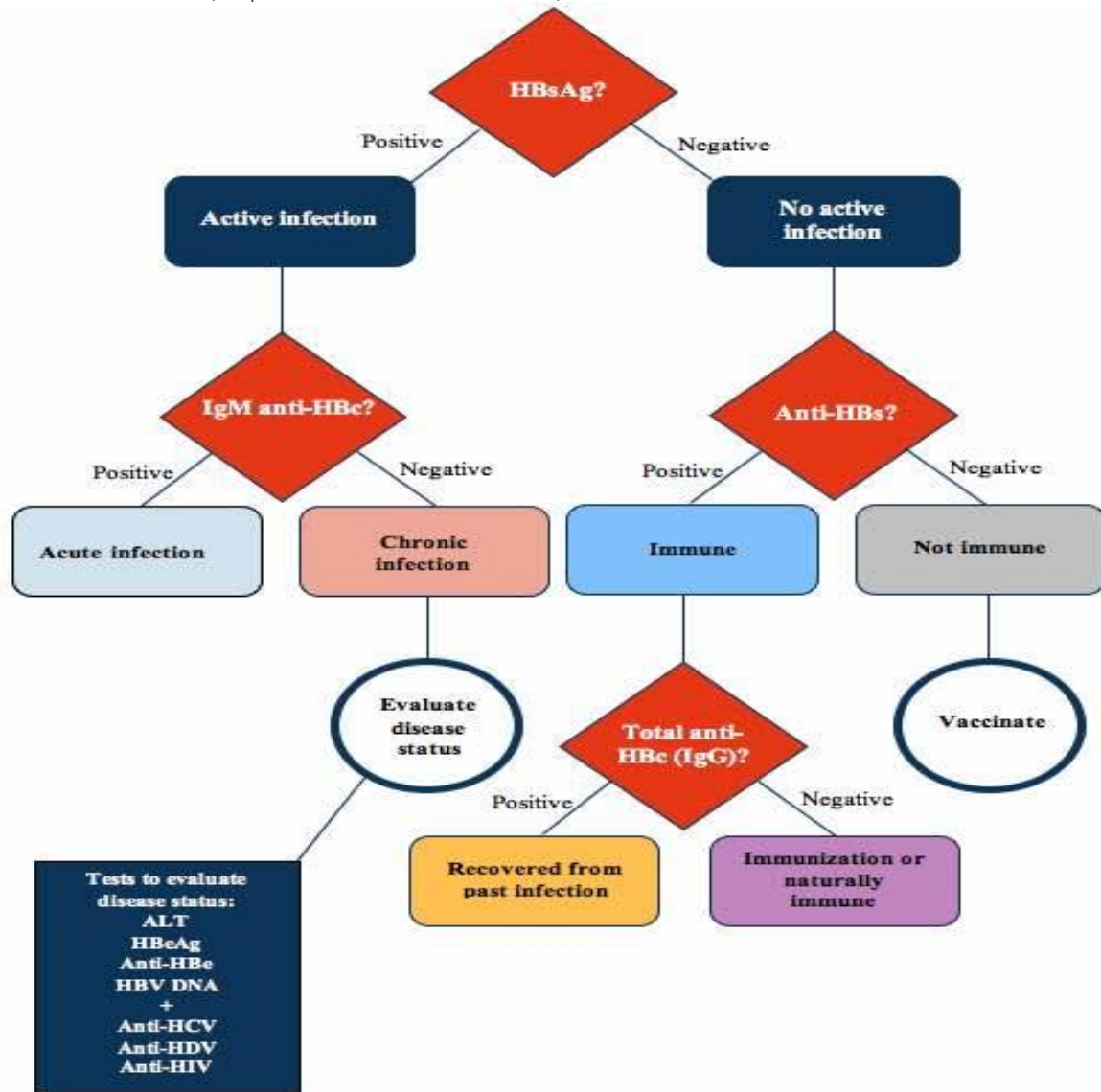
It is not possible, on clinical grounds, to differentiate hepatitis B from hepatitis caused by other viral agents and, hence, laboratory confirmation of the diagnosis is essential. A number of blood tests are available to diagnose and monitor people with hepatitis B. They can be used to distinguish acute and chronic infections.

Laboratory diagnosis of hepatitis B infection focuses on the detection of the hepatitis B surface antigen HBsAg. WHO recommends that all blood donations be tested for hepatitis B to ensure blood safety and avoid accidental transmission to people who receive blood products.

Acute HBV infection is characterized by the presence of HBsAg and immunoglobulin M (IgM) antibody to the core antigen, HBcAg. During the initial phase of infection, patients are also seropositive for hepatitis B e antigen (HBeAg). HBeAg is usually a marker of high levels of replication

of the virus. The presence of HBeAg indicates that the blood and body fluids of the infected individual are highly contagious.

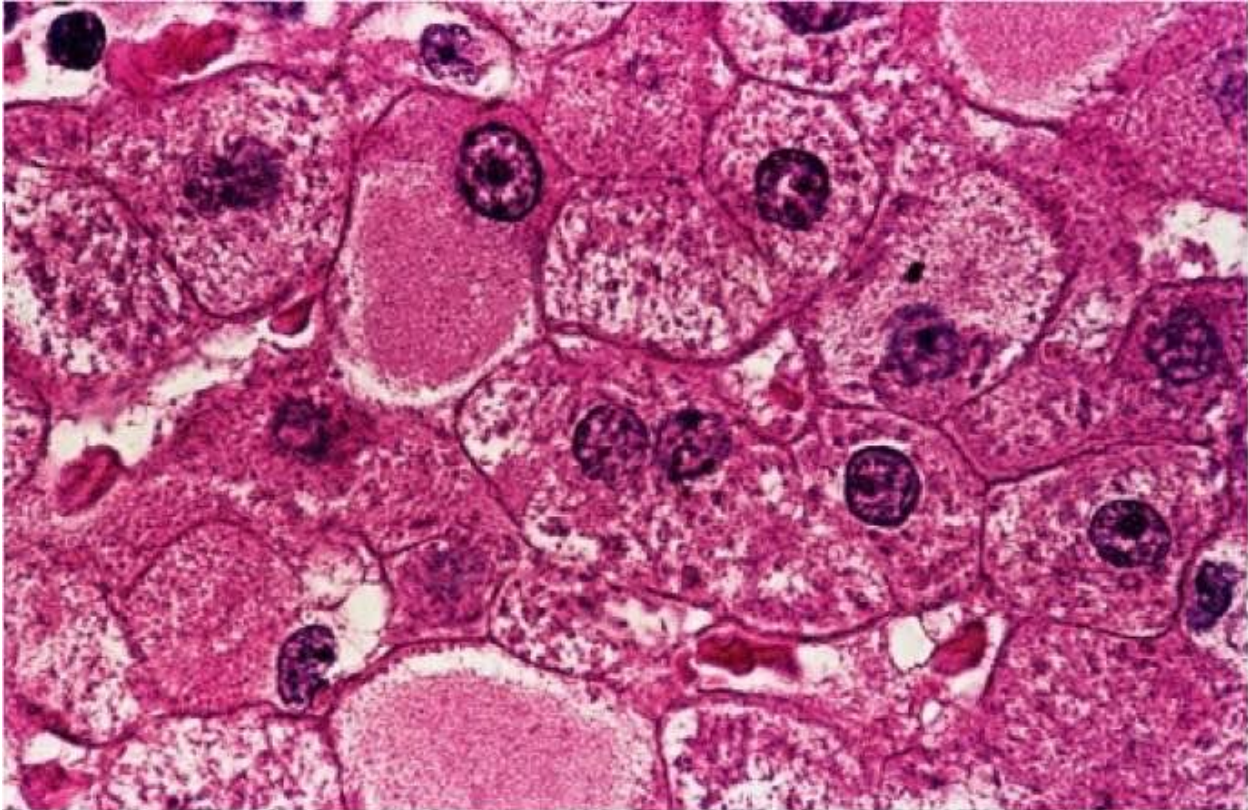
Chronic infection is characterized by the persistence of HBsAg for at least 6 months (with or without concurrent HBeAg). Persistence of HBsAg is the principal marker of risk for developing chronic liver disease and liver cancer (hepatocellular carcinoma) later in life.



Cytopathic effects: (22)

Little is known about the direct cytopathic effect of hepatitis B virus (HBV) and its association with particular viral genotypes or genetic mutations. We investigate HBV genotype–related differences in viral replication, antigen expression, and histopathology in severe combined immunodeficiency transgenic with urokinase-type plasminogen activator mice harboring human hepatocytes.

By using a humanized in vivo model, it shows that different HBV genotypes and even particular mutations resulted in different virologic and histopathologic outcomes of infection, indicating that particular genetic variants of HBV may be directly cytopathic in immunosuppressive conditions.



Control the virus and Prevention :

Testing & Vaccination

- The hepatitis B vaccine offers excellent protection against HBV
- . The vaccine is safe and highly effective. Vaccination consists of 3 doses of vaccine (shots) over the course of 6 months. Protection lasts for 20 years to life.
- The American Academy of Pediatrics recommends that all children should receive hepatitis B vaccine starting at birth. (AAP Policy).
- The CDC recommends hepatitis B vaccine for persons traveling to countries where HBV is common (2008 Yellow Book).
- Having one or more risk factors for hepatitis B infection, a simple HBV blood test should be taken. That will determine whether if the person is:
 - immune to hepatitis B; or
 - susceptible to hepatitis B and need vaccination; or
 - infected with hepatitis B and need further evaluation by a physician

- The basic test for acute HBV infection is called the "Hepatitis B Core IgM Antibody test." People who have acute hepatitis B show positive IgM antibodies on this test.

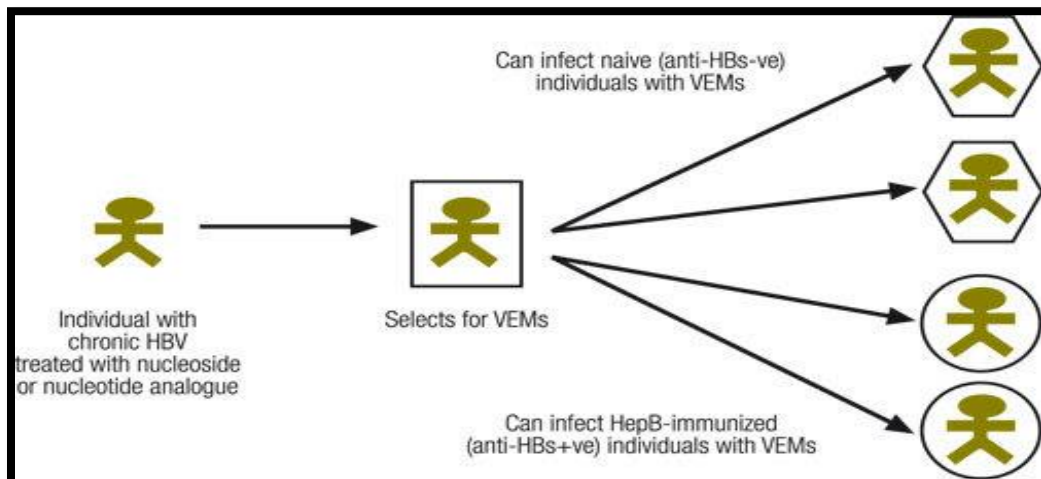
Perinatal Hepatitis

- California law requires testing of all pregnant women for hepatitis B infection
- If the mother is HBV-infected, she will pass the infection to the baby during the birth process, unless the baby gets immunized within hours of birth
- Giving the infant HBIG (hepatitis B immune globulin) and HBV vaccine right away will reliably prevent infection of the infant
- Other family members should best tested for hepatitis B too, and given vaccine if they are not already infected or immune.

Healthy Habits(prevention)

The best way to prevent hepatitis B is with vaccination. Other ways to reduce your risk of getting hepatitis B, hepatitis C, and HIV:

- When you inject drugs, stop and get into a treatment program. When you can't stop, never share needles, syringes, water, or "works"
- Do not share personal care items that might have blood on them (razors, toothbrushes)
- health people care or public safety worker, follow universal blood/body fluid precautions and safely handle needles and other sharps
- Consider the risks if when you are thinking about tattooing, body piercing, or acupuncture - are the instruments properly sterilized?
- And when you having sex with more than one steady partner, use latex condoms correctly and every time to prevent the spread of sexually transmitted diseases, including viral hepatitis and HIV.⁽²³⁾



Treatment:

Treatment for acute hepatitis B infection:

hepatitis B infection is acute — meaning it is short-lived and will go away on its own — may not need treatment. Instead, recommend rest and adequate nutrition and fluids while body fights the infection.

Treatment for chronic hepatitis B infection:

diagnosed with chronic hepatitis B infection, treatment is to reduce the risk of liver disease and prevent people passing the infection to others. Treatments include:

- Antiviral medications.
- Interferon alfa-2b (Intron A).
- Liver transplant.



Hepatitis B vaccine:

Vaccine type	Vaccines of this type on U.S. Recommended Childhood (ages 0-6) Immunization Schedule
Live, attenuated	Measles, mumps, rubella (MMR combined vaccine) Varicella (chickenpox) Influenza (nasal spray) Rotavirus
Inactivated/Killed	Polio (IPV) Hepatitis A
Toxoid (inactivated toxin)	Diphtheria, tetanus (part of DTaP combined immunization)
Subunit/conjugate	Hepatitis B Influenza (injection) Haemophilus influenza type b (Hib) Pertussis (part of DTaP combined immunization) Pneumococcal Meningococcal
Vaccine type	Other available vaccines
Live, attenuated	Zoster (shingles) Yellow fever
Inactivated/Killed	Rabies
Subunit/conjugate	Human papillomavirus (HPV)

Hepatitis B vaccine is made from parts of the hepatitis B virus. It cannot cause hepatitis B infection. The vaccine is usually given as 3 or 4 shots over a 6-month period.

Infants should get their first dose of hepatitis B vaccine at birth and will usually complete the series at 6 months of age.

All children and adolescents younger than 19 years of age who have not yet gotten the vaccine should also be vaccinated. There are no known risks to getting hepatitis B vaccine at the same time as other vaccines.⁽²⁴⁾

Medications:^(25 – 26)

- Several antiviral medications — including lamivudine (Epivir), adefovir (Hepsera), telbivudine (Tyzeka) and entecavir (Baraclude) — can help fight the virus and slow its ability to damage your liver.
- Interferon alfa-2b (Intron A). This synthetic version of a substance produced by the body to fight infection is used mainly for young people with hepatitis B who don't want to undergo long-term treatment or who might want to get pregnant within a few years. It's given by injection. Side effects may include depression, difficulty breathing and chest tightness.
- Liver transplant. If liver has been severely damaged, a liver transplant may be an option. During a liver transplant, the surgeon removes your damaged liver and replaces it with a healthy liver. Most transplanted livers come from deceased donors, though a small number come from living donors who donate a portion of their livers.

Other drugs to treat hepatitis B are being developed.



Host immune defense:

The immune response to infection with hepatitis B virus is directed toward at least three antigens: hepatitis B surface antigen, the core antigen, and the e antigen. The view that hepatitis B exerts its damaging effect on hepatocytes by direct cytopathic changes is inconsistent with the persistence of large quantities of surface antigen in liver cells of many apparently healthy persons who are carriers.

Additional evidence suggests that the pathogenesis of liver damage in the course of hepatitis B infection is related to the immune response by the host.

The surface antigen appears in the sera of most patients during the incubation period, 2–8 weeks before biochemical evidence of liver damage or onset of jaundice. The antigen persists during the acute illness and usually clears from the circulation during convalescence. Next to appear in the circulation is the virus-associated DNA polymerase activity, which correlates in time with damage to liver cells as indicated by elevated serum transaminases. The polymerase activity persists for days or weeks in acute cases and for months or years in some persistent carriers. Antibody to the core antigen is found in the serum 2–10 weeks after the surface antigen appears, and it is frequently detectable for many years after recovery. The titer of core antibody appears to correlate with the amount and duration of virus replication. Finally, antibody to the surface antigen component appears.

During the incubation period and during the acute phase of the illness, surface antigen-antibody complexes may be found in the sera of some patients. Immune complexes have been found by electron microscopy in the sera of all patients with fulminant hepatitis, but are seen only infrequently in nonfulminant infection. Immune complexes also are important in the pathogenesis of other disease syndromes characterized by severe damage of blood vessels (for example, polyarteritis nodosa, some forms of chronic glomerulo-nephritis, and infantile papular acrodermatitis) . (27)

Genetics (gene mutation):

HBV X is considered to be the smallest of four kinds of HBV functional genes, but it conveys a 154-amino-acid multifunctional protein (HBx), with an N-terminal negative regulatory/antiapoptotic domain and a C-terminal transactivation/proapoptotic domain. The gene also seems to be associated with modulation of a wide range of cellular functions, leading to HCC. Besides, of the four open reading frames, the X gene remains unknowable. There are conflicting suggestions about the functional activity of HBx. HBx induced HCC in certain transgenic mice *in vivo* and *in vitro*. However, there are other transgenic lineages in which HBx does not lead to HCC development. HBx is a multifunctional regulatory protein that interacts with a variety of targets and mediates many cellular functions directly or indirectly. Thus, the goals of the present study were to explain the characteristics of HBx mutations according to the clinical phase of HBV infection and to examine the functions of significant HBx mutations that appear to be related to HCC pathogenesis (28)

X is an enigmatic HBV protein, necessary for efficient infection and replication *in vivo*. HBx is known to exhibit a transcriptional transactivation function for many viral and cellular genes and is therefore required for efficient transcription of viral RNAs from cccDNA in infected hepatocytes. Since it has no DNA-binding activity, its transactivation function is manifested through interaction with cellular factors.

It was suggested that HBx protein had a role in HBV-induced carcinogenesis by number of different mechanisms. However, the role of specific mutations in the X gene is not yet well characterized. Some of X gene mutants and also deletions of this region have been described in patients with hepatocellular carcinoma. Integration of HBV genomic DNA into cellular chromosomes

commonly occurs during the viral life cycle and is observed in most chronic hepatitis samples and in 86.4% of HBV-related HCCs. Upon integration of HBV DNA in host genome, the 3'-end of the HBx is often deleted. This truncation of C-terminal region of HBx protein was shown to play an important role in HCC development through promotion of oxidative stress and induction of mitochondrial DNA damage.

Precore messenger RNA (mRNA) encodes HBeAg. Core mRNA encodes the core protein (the major nucleocapsid protein), DNA polymerase (which reverse transcribes the RNA pregenome), and serves as the pregenomic RNA, the template for reverse transcription. A variety of precore/core mutants have been described. The 2 well-defined precore mutations include a stop codon mutation at nucleotide (nt) 1896 (or codon 28) (resulting in the cessation of HBeAg expression) and mutations in the basal core promoter (BCP) at nt 1762 and nt 1764 (resulting in diminished production of HBeAg and a resultant increased host immune response). Precore mutations frequently occur temporally related to core gene mutations/deletions. Core gene mutations are epidemiologically associated with disease activity whereas the precore stop mutation may be an innocent bystander. In contrast, precore mutations in the BCP are likely to increase viral replication and enhance disease activity ⁽²⁸⁾

Recent discoveries:

[Prevalence of antibody to Hepatitis B core antigen and Hepatitis B virus DNA in HBsAg negative healthy blood donors](#)

Hepatitis B virus is one of the most important blood born viruses. Although the sensitivity of screening tests has been considerably increased, transmission may still occur due to window period or occult hepat...

Gharib Karimi, Maryam Zadsar, Nasrin Vafaei, Zohreh Sharifi and Mohammad FalahTafti

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