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An Introduction To Chronic Hepatitis Virus

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Introduction

The five main strains of the Hepatitis Virus lead to inflammation of the liver, along with a wide range of health problems, that can potentially be fatal ("Hepatitis"). The five main strains of the Hepatitis Virus are A, B, C, D, andE, that consist of a similar target organ but differin types of symptoms, side effects, mode of transport, and treatments. The main hepatitis related deaths are through liver cirrhosis, Hepatocellular Carcinoma (liver cancer), and Fibrosis, which are most commonly caused by chronic Hepatitis B and C. In the United States, over 3.5-5.3 million individuals live with thechronic strand of viral Hepatitis, in which symptoms are suppressed until severe liver damage has occurred (Liang). The liver is an essential organ that is required to filter blood, detoxicate the system, and absorb vital nutrients for healthy function of the body. Hence, damageto the liver prevents quintessential functions from occurring. While hepatitis or damage to theliver can be caused by various ways of intoxicating the system such as excessive alcohol intake or medication, the more severe and direct method is through the infection of the Hepatitis B or Hepatitis C viral strand. While both chronic viruses cause hepatitis, the manifestation, mode of transport, severity, and treatments can defer vastly. With this in mind, the most effective methods of research in this field are done through the use of In-Vivo Model Systems for Hepatitis. In-Vivo systems include

Primate models, Tree Shrew models, surrogate models such as Mice (Ortega-Prieto). Essentiallyspeaking, In-Vivo models refer to research conducted within a living organism, in this case for human chronic hepatitis. This being said, the predominant goal behind research in the liver infectious diseases is to identity successful and supplementary vaccines and medication through further understanding the disease as a whole,and being able to test long-term effects, sideeffects, and efficiency of proposed treatments; which can potentially vary according to demography, environment, age-groups, and economical limitations within the research field.

Hepatitis B Virus (HBV)

Hepatitis B is known as a "vaccine-preventable liver infection" that is caused by the Hepatitis B Viral strand ("Hepatitis B"). This disease can manifest itself in a mild form that lasts a couple weeks but also has a high potential to manifest as a life-long/chronic condition; and is highly likely to be so for unvaccinated infants later on in theirlife ("Viral Hepatitis"). The virus itself is spread in humans through the contact of bodily fluids such as blood and semen. Such transmissions can occur through birth from an infected mother,sexual activity with an infected individual, use of contaminated instruments, as well as blood transfusions ("Viral Hepatitis"). Although not all, for those that do showcase symptoms, it may

include fatigue, jaundice, loss of appetite, and nausea. In the cause of chronic hepatitis viruses, this can be manifested in the form of liver canceror scarring of the liver tissue, which in turn disrupts proper function of the liver organ in the human body. A vaccine for this type of Hepatitis has been developed for all age groups, known as the HepB surface antigen, or HBsAg, and is efficient through the recombinant DNA technology; this can be given as a single stand-alone vaccine or as a combinations vaccine along with other targeted diseases ("Hepatitis B"). The HBsAg is the surface antigen that patients are tested for in order to determine the presence of the Hepatitis B virusin the system. The administration of the surface antigen itself creates an immune response in the human system, leading to protection against the Hepatitis B Virus in general. However, it is important to note that a major limitation to the administration and development of such vaccines are the lack of economical and materialresources in the field. Nevertheless, the HBsAg Vaccine has yielded as mostly successful towards preventing the infection of the Hepatitis B virus in humans (CDC 4).

The molecular structure of the Hepatitis B Virus is a partially double-stranded DNA (Deoxyribonucleic Acid) with the reverse transcriptase enzyme for the RNA intermediate to be transcribed. This is an enveloped, icosahedral virus that contains a circular dsDNA(double-stranded DNA) genome in the nucleus (Venkatakrishnan). The lipid envelope consists of the HBsAg protein that surrounds the viral HBcAg complex in the DNA genome, within the nucleocapsid ("Hepatitis B"). The genome consists of instructions, and encodes for fourmain Open Reading Frames (ORFs). Open Reading Frames are sequences in the codons thatdon't contain a stop codon that functions as a stop signal; usually it is the region between the start and stop codons in the sequence. Specific for the Hepatitis B virus, the ORFs are S, C, P, and X. Briefly, the S frame codes for the structural proteins in the envelope of the virus, including the HBsAg complex. S (surface), C (core), P (polymerase) and X (X protein) and include 7 proteins that are also essential for the life cycle of the virus. This aids towards the structure and efficient function of the virus as a whole. The C ORF encodes for content within the nucleocapsid, HBcAg or HBeAg (Hepatitis B e Antigen). Essentially, the HBeAg supplements continuous infection of the virus to the host, Followed by ORF P, encodes a large protein consisting of 800 amino acids in which has three main functions: terminal protein function, reverse transcriptase function, and the ribonuclease H domain. Finally, the X ORF encodes a protein that initiates general cell functions such as DNA repair, inhibition of protein degradation, and activation of certain processes ("Hepatitis B").

The Hepatitis B virus belongs to the Hepadnaviridae family, which usually infects and replicates in hepatocytes. Hepatocytes are the cells within the main tissue of the liver (Zhao). To begin, the virus binds to the Heparan Sulfate Proteoglycans, which are essentially cell surface glycoproteins, as the first step of theinfection. At the same time, receptors on the surface of the host cell along with proteins from the virus initiate and trigger internalization of the viral genome. In which, through endocytosis,the viral DNA containing nucleocapsid is released into the cytoplasm of the host cell. Once this occurs, the nucleocapsid disassembles,encoding the viral genome into the host's genome in most cases, through the nuclear pore complex. Now, with the use of the Host's RNA Polymerase II, the genome intermediate is used to generate the future Hepatitis B Virus sequences within the host's system (Zhao).

Clinical treatments for the Hepatitis B virus include a variety of immune modulator drugs and antiviral drugs. The immune modulator drugs are given as vaccination shots that boost the immune system, potentially terminating/preventing the Hepatitis B virus. On the other hand, the antiviral drugs terminate or slow down the reproduction of the viral sequence within the host system, which can reduce the inflammation of the liver. In chronic conditions, such as Hepatitis B, antiviral drugs may need to be taken for an extended duration oftime, in order to reduce the inflammation of the liver to an appropriate level for the host to survive. Research for a complete cure is still being developed, given the limitations in clinicaltrials and resources available for this disease. Nevertheless, recent and promising In-Vivo models that have been used for Hepatitis B research include: Chimpanzees, the only primatemodel available for HBV research, vaccines for human HBV were derived through the discoveryof long-term protective immune responses in Chimpanzees, Tree Shrews, the only non-primate species available for HBV research,which has been found to be susceptible towards similar strands to the human HBV, and surrogatemodels, such as American Marmota Monax, thathave led to more efficient and simplified opportunities for research in the Hepatitis B field (Ortega-Prieto). In general, the main limitations to this type of Hepatitis, given the severity and chronic characteristics, are the necessary resources to successfully test long-term responses and appropriate treatments based on complications and population type.

Hepatitis C Virus (HCV)

Hepatitis C virus is also a type of virus that leads to the inflammation of the liver organ in the human system, caused by the Hepatitis C Virus strand. Similar to Hepatitis B, the C type can also vary from short term illnesses to long-term chronic diseases in humans ("Hepatitis C"). However, the main difference isthat there is no vaccine to prevent Hepatitis C, asthere is such for HBV. This being said, the preventive methods for this virus are limited to restraining from coming into contact with contaminated surfaces and substances. The mainmethod of transmissions of HCV is through contact with infected blood, semen, or other bodily fluids, through childbirth, use of contaminated instruments such as needles. This being said, the main symptoms of hepatitis C virus include, loss of appetite, fever, fatigue, abdominal pain, joint pain, and nausea (CDC previous).

The Hepatitis C virus is an enveloped, positive-strand RNA virus that consists of glycoproteins within the envelope, lipid membranes, and nucleocapsid containing the single-stranded RNA viral genome (Structure). The envelope of the virus consists of two glycoproteins, E1 and E2 glycoproteins. The E2 protein protects the E1 protein from the immune system, enabling successful host-receptor binding, membrane fusion, and ultimately assembly of the viral genome. Furthermore, the lipid membrane is mostly composed of cholesterol, cholesterol esters, and other lipid-like substances in the virus. It has been found that the cholesterol in the lipid membrane of the virus enables the entering and assembly ofthe infection cell and system as a whole. Followed by the capsid or core, that plays a role in protecting the viral RNA, and are made by theHepatitis C core protein. These proteins interact with each other in order to reach successful assembly, as the HCV RNA and envelope E1 protein receive signals to bind to the surroundings. Moving on the RNA genome itself, its classifications illustrate that it can be used for both translation and transcription given the presence of the RNA genome, along with an internal ribosomal entry site that regulates the entry and binding of the viral genome to the translation factors of the host. The HCV virus strand contains ten major proteins that play a role in efficient host cell infection. The first protein that comes across as essential is the Coreprotein, which ensures the formation of a viral capsid, including the structure to protect the viral RNA genome. The core protein is the first protein to get translated during the process of translation. This is followed by the E1 and E2 glycoproteins that play a role in the replication cycle along with the binding of the viral genometo the host cell. Next in line is the P7 protein, that is also involved in the viral assembly and release from the virus to the host cell. Then, nonstructural proteins 2, 3, 4 and 5 participate inthe host-cell interaction, enzyme activity, cofactors, and in general, catalysis of essential processes and requirements for the life cycle.

There are nine brief steps involved in the life cycle of the Hepatitis virus. Starting withthe binding of the virus to the surface of the hostcell through the Low Density Lipoprotein Receptor (LDLr) and Heparin Sulfate Proteoglycans (HSPGs). Then, this initiatesfolding of the viral particle into the hepatocyte cell membrane, commonly known as the processof endocytosis. Once this occurs, the virus particle uncoats the outer layer, and is free to move within the cytosol, a liquid found inside the cell, within the endosomal vesicle. This is when the process of translation and replication can take place. The translation process takes place along with the ribosomal subunits, in which a single polyprotein is created. Then, afterthe proteins are processed in the endoplasmic reticulum of the cell, RNA replication takes place. The RNA replication process is aided by the HCV nonstructural proteins. This is followedby the process of assembly, in which the HCV particles assemble at a specific point, and are filtered based on maturation in order to be released within the cell. In the Golgi, maturationof the particles takes place, preparing its release.Finally, the multivesicular HCV viral particles approach the cell surface, in which they fuse to the cell membrane. These particles are then released into the rest of the cell, through which the infection spreads ("Hepatitis B").

While symptoms for Hepatitis C virus may remain suppressed or may manifest itself indiseases related to the liver, there are also extrahepatic manifestations of the virus that could lead to other complications. Diabetes mellitus[1], Glomerulonephritis[2], Essential mixed cryoglobulinemia[3], Porphyria cutanea tarda[4], andNon-Hodgkin's lymphoma[5] are all medical conditions that could be developed due to a HCV infection ("Hepatitis C"). Hepatitis C can be managed using direct-acting antiviral (DAA) tablets, reducing the damage imposed on the liver in the human system. It has also been advised that patients at risk of chronic Hepatitis C Virus should be vaccinated with Hepatitis A and B vaccines, to prevent development of further medical conditions (NHS Choices).

Ideally, when such viruses attack the system, this should trigger the activation of the body's innate immune response

system. Which is a nonspecific defense system that works as thefirst line of defense during any viral attack or infection. There are four types of defensive barriers that can be activated as a part of the innate immune system based on the types of signals the body receives: anatomical, physiologic, endocytic/phagocytic, and inflammatory systems. Anatomical includes the formation of skin and mucous membranes, physiological includes changes in body temperature and pH, endocytic and phagocytic involve the proteins within the body, andinflammatory involves the body's cells to heal a wound. In the case of the Hepatitis virus, a specific pathogen recognition receptor (PRRs) recognizes the strain of hepatitis virus and triggers the innate immune response system, which includes the production of interferons (IFNs). Interferons are an antiviral factor synthesized by the white blood cells that essentially interrupts the replication process of the virus. A common signaling pathway for these types of pathogens begin with the TLR proteins at the surface of the cell that get activated in the presence of various parts of the pathogen, such as DNA, RNA, strand type, and proteins. These TLR proteins are present both in the surface and in the endosome of the cell, so that detection of the virus can be made at the initial stage of infection or during endocytosis. In the liver, the hepatocytes are in charge of synthesizing the innate immune proteins for defense. With this in mind, the second signaling pathway includes the detection of double-stranded HBV particles in the cytosol of the cell. This is done using the Retinoic Acid Inducible gene I (RIG-I), which binds to theHBV dsRNA particles, essentially inhibiting/disturbing the production of essential proteins and processes. Then, the interferons bind to a receptor on the surface of the cell that activates the JAK-STAT pathway of the immunesystem.

Conclusion

All in all, the chronic hepatitis virus B and C are diseases that are still being researched about, and have treatments that are being improved and developed to better suit various populations. Along with political and economical limitations, ethical and moral values also need to be considered when carrying out clinical trials for such viruses.

References

[1] Diabetes mellitus: affects the usage of blood sugar within the body
[2] Glomerulonephritis: inflammation of the filterswithin the kidney
[3] Essential mixed cryoglobulinemia: form of inflammation of blood vessels and restrictive blood flow
[4] Porphyria cutanea tarda: skin lesions
[5] Non-Hodgkin's lymphoma: lymphatic cancer

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