Undergraduate Review

Volume 11 Article 8

2015

Exploring the Human Hepatocirrhosis Virus

Dawilmer Castillo
Bridgewater State University

Exploring The Human Hepatocirrhosis Virus

Dawilmer Castillo

The Human Hepatocirrhosis Virus (HHV) infection of human hepatocyte cells leads to massive cell death that ultimately causes liver failure, a life threatening condition that demands urgent medical care. In the United States alone, HHV is responsible for approximately 2,800 deaths each year and causes irreversible tissue damage that affects over 8,200 people that will require lifelong treatment. Most often, liver failure occurs gradually over many years following HHV infection. The symptoms of the disease are swollen abdomen, mental disorientation, and even coma. To prevent infection from the HHV virus one should practice proper hygiene and safe sex and avoid consuming contaminated food and water. Understanding the functions, structure, mechanical processes and characteristics of HHV is crucial for early detection, treatment, and the development of a potential vaccine for the virus.

Pathology

HHV enters the human body through the mucosa of the mouth, nose, genital area, or open wounds in the skin; however, most infections originate from consumption of contaminated food or water. After the virus enters the body, it travels through the bloodstream until it reaches the hepatocytes in the liver (Figure 1a). Once it encounters the hepatocytes, HHV infects cells by binding to a specific receptor unique to hepatocytes and starts making copies of itself. The newly assembled viral particles exit the host cell and propagate into neighboring hepatocytes, causing massive cell death. This activates the immune system, which fight the spread of the virus and causes inflammation of the liver (Figure 1b). Since HHV propagates very fast it mutates frequently thus preventing the body from building long-lasting immunity to the virus. The viral infection and the constant release of chemicals by the immune system results in cirrhosis of the liver. Histologically, the HHV damage resembles liver damage by Hepatitis viruses, as shown in Figure 1. The liver does not have sufficient time to heal itself thus forming cirrhotic tissue. A cirrhotic liver cannot effectively synthesize proteins, filter the blood or regulate blood sugar levels. If left untreated, the loss of liver functions may cause death and other serious complications such as cancer. 8

Virion Characteristics

The Human Hepatocirrhosis Virus is an enveloped virus with icosahedral shape (Figure 2a) with an approximate size of 40 to 60nm. The virus also has the tegument, comprised of proteins that line the space between the envelope and the nucleocapsid (Figure 2b). These proteins mainly contribute to viral RNA replication, the elimination of cellular competition and the evasion of the immune response. Dawicasmer12 (DCM12) and Rocasmer14 (RC14) are glycoproteins present on the surface of the envelope and play an important role for viral attachment and entry to the host cell (Figure 2c). HHV has a negative sense single stranded RNA genome, which is linear and nonsegmented. The genome is relatively small (95kB), thus the virus has evolved several mechanisms to code as many functional proteins as possible as discussed below.

Virus Life Cycle and Interaction with Host Cell

After HHV enters the human body, the virus glycoprotein ligands (DCM12 and RC14) will bind to complementarily receptors on the surface of hepatocyte cells named DCM12-C and RC14-C. Next, the host cell engulfs the virion via enclosure into the cellular membrane forming a vesicle and intaking the HHV virus into the cytoplasm of the cell in a process called receptor-mediated endocytosis. Once inside of the cell, HHV will activate its M2 channels that will change the pH of the intracellular environment, disassociating the virion envelope, capsid and cellular vesicle. Release of the HHV RNA genome into the cytoplasm will start viral protein synthesis and replication using cellular machinery (Figure 3). The replicated HHV genome is packaged inside a newly synthesized capsid. The virus maturation and release will then follow with new HHV virions exiting the host cell via budding. The release of new HHV progeny allows for further infection of healthy cells, repeating the process (Figure 4). 5, 6

HHV Replication and Translation

HHV needs a RNA-dependent RNA-polymerase to replicate its negative sense ssRNA genome, an enzyme not found in animal cells. The virus codes for its own RNA-dependent RNA-polymerase and packages a functional enzyme in each virion. To start replication, the viral polymerase complex reads the (-)ssRNA genome 3' to 5' direction and it synthesizes the complementary (+)ssRNA strand 5' to 3' direction. The same polymerase complex will then read the (+)ssRNA and synthesize a new complementary (-)ssRNA strand (Figure 5a) which is then ready to be packaged in a capsid. 6

The virion RNA is negative sense (complementary to mRNA) and must therefore be copied into the complementary (+) ssRNA before viral proteins can be synthesized. (+)ssRNA is the same sense as cellular mRNA so it functions as a regular mRNA molecule. The newly synthesized viral (+)ssRNA

Effects of Viral Infection in the Liver

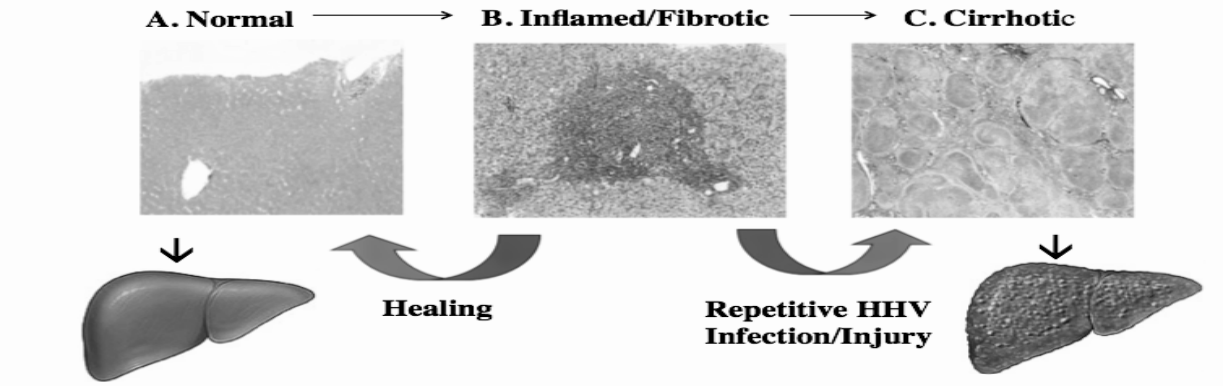

Figure 1. Histological appearance of hepatocytes isolated from an individual infected with HHV at different stages of progression during viral infection. A) Micrograph depicts normal/healthy liver tissue before viral infection; (B) inflamed/fibrotic tissue as occurs upon infection; and (C) cirrhotic hepatocytes after repetitive exposure to HHV and the activation immune system.

Virion Characteristics

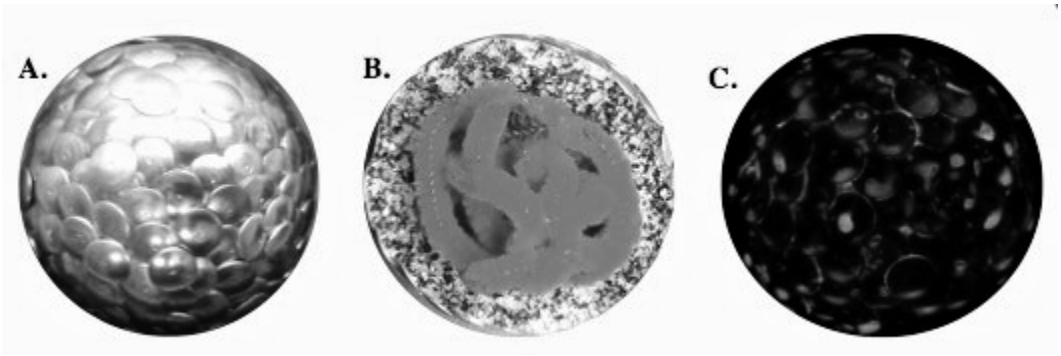

Figure 2. Model of the Human Hepatocirrhosis virus.
A virion constructed by using a 4-inch Styrofoam white ball and manually pinning gold and silver thumbstacks in a circular pattern. (A) The envelope of the virus is depicted by different thumbstack colors to represent the different proteins found in the envelope of the virion; (B) is a cross section image of the HHV virus made by cutting a Styrofoam white ball in half and painting the inside with black marker to represent the viral tegument. A red nylon chenille stem was then glued in the middle of the styrofoam ball which represents the -ssRNA genome of HHV that is encapsulated by the capsid (not depicted); (C) is a HHV model stained with green fluorescent dye (glow stick liquid) to represent the glycoproteins present on the surface of the virus used for identification of hepatocyte cells.

can be translated by cellular ribosomes resulting in protein synthesis (Figure 5b). It is critical for HHV to code for RNA-dependent RNA-polymerase in its genome and also package it in the virion capsid so that the polymerase can synthesize (+)ssRNAs upon infecting the cell so that translation and replication can occur. 6

Evolutionary Gadgets

HHV has a relatively small genome thus it can only code for few proteins. To overcome this, HHV has evolved several traits that allow it to compensate for its small genome and successfully compete with cellular molecules. HHV is polycistronic, meaning that a single viral mRNA molecule encodes for several different polypeptide chains. When the viral mRNA gets translated into proteins, multiple proteins are bound together. The viral mRNA is translated into large molecules in which multiple proteins are connected together into a polyprotein. Enzymes called proteases cleave the huge polyprotein resulting into separation of the individual pieces. HHV also encodes for viral de-capping enzymes that degrade

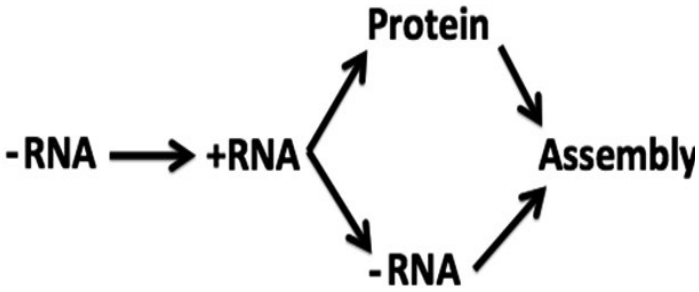

Figure 3. Schematic of the mechanism for HHV viral replication and protein synthesis. The HHV virus has a (-) ssRNA DNA that is synthesized into its complementary (+) ssRNA strand. The (+) ssRNA strand can then be translated (protein synthesis) by cellular machinery and replicated (formation of a newly synthesized viral genome). This results in the assembly of a new virus which will exit the host cell and infect new cells.

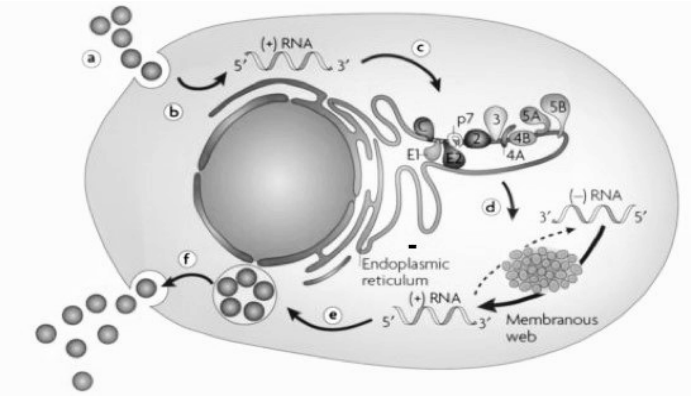

Figure 4. Schematic of HHV lytic life cycle and virus/host interaction at the cellular level. a) Virus binding (adsorption) and internalization (penetration, entry), b) cytoplasmic release and uncoating, c) IRES-mediated translation and polyprotein processing that directs the virus to the host endoplasmic reticulum, d) RNA replication (biosynthesis), e) packaging and assembly, f) virion maturation and release.4

the CAP structure of cellular mRNAs preventing them from being translated. This allows HHV mRNAs to be translated faster than cellular mRNAs. The virus can also use the CAP from the degraded cellular mRNAs and add it to its own mRNA molecules. 6 In addition, the viral mRNA has internal ribosomal entry site (IRES). This is a unique structure in the mRNA molecule of the virus allowing it to bypass the need of a CAP at the 5' end of the mRNA molecule in order for translation to occur. Thus, cellular machinery would translate the sequence because IRES will mimic the CAP structure. Viral polyA polymerase adds a poly-A tail to all viral mRNAs. These evolutionary gadgets allow HHV to replicate and synthesize proteins efficiently by utilizing cellular machineries. 6

Immune Response and Genomic Changes

Due to a high mutation rate during HHV replication, the immune system is relatively inefficient. The lack of proofreading activity during viral replication results in genetic

HHV Replication and Translation

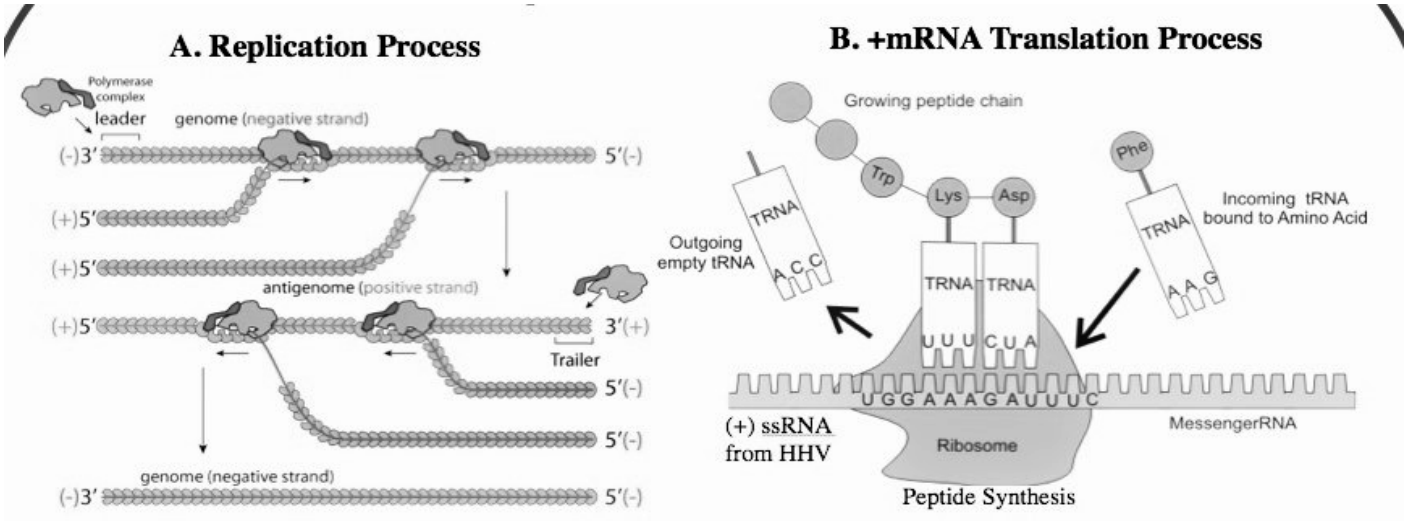

Figure 5. Schematic of HHV replication and translation. HHV has its own transcription and replication factors that allows proper synthesis of (-)ssRNA copies and proteins. (A) The (-)ssRNA from HHV gets synthesized to (+)ssRNA by a polymerase complex. Once it is a (+)ssRNA strand, the polymerase complex can replicate a new (-)ssRNA strand.9 (B) The complementary (+)ssRNA is translated and different proteins are synthesized using cellular machinery.1 The diagram in panel A originally appeared in Viralzone/Expasy database9.

drift, which is the change in the frequency of a gene variant in a population. The majority of these mutations continuously change the structure of the HHV virus, resulting in an activation of a new immunological response for the same virus. Thus, the antibodies that initially recognize and attack HHV no longer activate the immune system, therefore the immune system has to generate new antibodies, which takes time. By then, the virus has already gained new mutations, therefore, repeating the cycle. HHV can also inhibit the expression of the major histocompatibility molecule I (MHC I), which displays fragments of viral proteins from within the cell to the cell surface so that the immune system can then identify and attack the infected cell. Without MHC I the cells of the immune system become practically blind for the virus. By inhibiting MHC I, HHV is allotted more time to propagate under the radar of the immune system, thus causing extensive damage to the liver. 6

Currently, there are no vaccines to combat this pathogen, however, there are medications that can decrease the propagation rate of the virus to new cells. A hypothetical antiretroviral drug called Dawilcasmer prevents HHV infection by binding to the hepatocyte receptor (DCM12-C), which unable the virus from binding to this glycoprotein and entering the host cell. HHV receptor DCM12 has to complimentary bind to a DCM12-C receptor in hepatocytes in order to enter the cell. However, this interaction gets disrupted by Dawilcasmer that acts as antagonist molecule that binds to the DCM12-C receptor, preventing the HHV from binding to the DCM12-C receptor and entering the cell. 2

Acknowledgements

The author would like to express his gratitude and appreciation to the Office of Undergraduate Research for sponsoring the Virtual Virus project via the ATP Course-Embedded Grant and to his mentor, Dr. Boriana Marintcheva, for her inspiring guidance and invaluable constructive criticism.

Bibliography

1 Boundless. "Structure and Role of Ribosomes." Boundless Anatomy and Physiology. Boundless, 25 Nov. 2014. Retrieved 10 Dec. 2014 from https://www.boundless.com/physiology/textbooks/boundless-anatomy-and-physiology-textbook/cellular-structure-and-function-3/translation-to-a-polypeptide-52/structure-and-role-of-ribosomes-360-11674/

2 Dennis Sifris, MD and James Myhre. (2014, May 13). CCR5 Receptor Antagonist - Definition - HIV/AIDS. Retrieved February 2, 2015, from http://aids.about.com/od/hivaidsletterc/g/Ccr5-Receptor-Antagonist.htm

3 Husney, A., & London, T. (2014, March 12). Cirrhosis of the Liver. Retrieved December 10, 2014, from http://www.webmd.com/digestive-disorders/cirrhosis-of-the-liver

4 Moradpour D, Penin F, Rice CM. Replication of hepatitis C virus. Nature Reviews Microbiology 2007;5:453–63, from http://www.medscape.com/viewarticle/751417_2

5 Productive Life Cycle of Animal Viruses Animations - Library. (2013, July 22). Retrieved November 20, 2014, from http://www.microbelibrary.org/library/virus/3205-productive-life-cycle-of-animal-viruses-animations

6 Shors, T. (2013). Understanding viruses. Burlington, MA: Jones & Bartlett Learning.

7 Stages of Liver Disease - HepCBC. (n.d.). Retrieved December 10, 2014, from http://hepcbc.ca/stages-of-liver-disease/

8 The progression of Liver Disease. (2011, October 4). Retrieved November 18, 2014, from http://www.liverfoundation.org/abouttheliver/info/progression/

9 ViralZone: Negative stranded RNA virus replication. (n.d.). Retrieved December 10, 2014, from http://viralzone.expasy.org/all_by_protein/1096.html

About the Author

Dawilmer Castillo is a graduating senior majoring in Biology and minoring in Biochemistry and Spanish. His research project was completed in the fall of 2014 under the mentorship of Dr. Boriana Marintcheva (Biology) and made possible with funding provided by the Office of Undergraduate Research through a course-embedded research grant. Dawilmer plans to pursue his M.D. in the fall of 2015.