

The Ebola Wars

General Edition

by

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In every battle there comes a time when both sides consider themselves beaten, then he who continues the attack wins.

—Ulysses S. Grant—

Part I –What Is a Virus?

“I can’t believe I’m a college sophomore,” thought Terry in amazement while taking the train back home for the summer. “The school year went by so fast, but I made it through even though I had to change my major.”

A text popped up on Terry’s smartphone, “Terry, when r u going on ur trip? Let’s meet up before u go.” Terry recognized that the message was from Alex, a long-time friend from high school. “Leaving in a week,” Terry quickly texted back. “Never been on a trip outside of the US and can’t wait to work with doctors and nurses to help sick people. Alex, let’s meet up Fri.”

After a week of seeing family and friends, Terry was off to the west coast of Africa for ten weeks. This would be a life-changing experience. The agency placed Terry in a rural site where residents had limited access to medical care. The locals sometimes traveled miles to be seen at their clinic. The health care professionals on the team were unbelievably positive and devoted to educating and providing patients with the best care possible. Residents came in with many types of ailments. Terry’s responsibilities included greeting patients and their families, bandaging wounds, and providing additional assistance to doctors and nurses as needed.

Just like the school year, the summer experience seemed as though it was over in no time. Terry was about to return home when unexpected news came. Terry’s team was contacted by the Centers for Disease Control and Prevention (CDC) and notified that they had likely been exposed to a patient infected with the Ebola virus as there was an outbreak near the medical relief site. The patient who had contracted the virus had died. Struck with fear, Terry quickly tried to determine which patient it could have been and her likelihood of being infected, but she found this nearly impossible to figure out. As a precaution, all individuals on the team returning to the US had to be screened and undergo a 21-day quarantine where they would be monitored for any Ebola-like symptoms. Not doing so could potentially place others at risk for contracting this deadly virus.

“I need to find out more about viruses so that I can understand what’s going on,” thought Terry as she reached for her general biology textbook. Glancing through the section on virology, she was surprised to discover that viruses are tiny particles considered to be non-living since they cannot metabolize energy, do not create waste, do not grow, and require host cells to multiply. Indeed, in order to replicate, viruses hijack the machinery present within the cells that they infect. The additional viral particles produced inside host cells can exit and infect other cells. “These viruses seem kind of creepy,” thought Terry. “They’re like parasites to cells.”

Terry continued reading:

Viruses have either a DNA or RNA genome, which can be single- or double-stranded. These genomes are housed in a capsid made of proteins. Viruses can be classified by their specific genomes and the unique features of their capsids, including shape and protein constituents. Some viruses have lipid envelopes derived from host membranes that enclose the virus particle, while others do not. Surface glycoproteins on these membranes, or spike proteins protruding from the viral capsid in non-enveloped viruses, can play a role in viral attachment and entry into the host cell.

Terry spent the next few minutes summarizing the information she had just read.

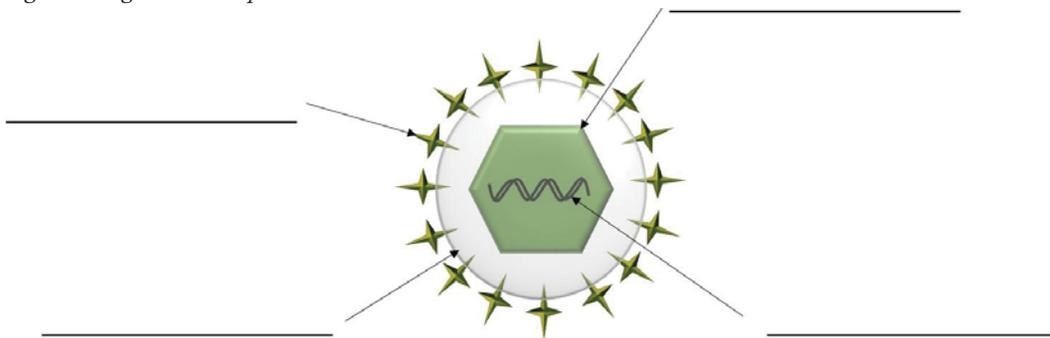
Questions

1. Which structural features are in common to all viruses, and which are not? Complete the table below to answer this question based upon the information provided in the case.

<i>Shared Attributes</i>	<i>Differences</i>

2. Why are viruses considered parasites?
3. Examine the diagram of the viral particle below. Label all of the important structures on this virus that you identified in the table above.

Figure 1. A general viral particle.



4. Design an imaginary viral particle. Create a diagram of your virus and label its major features. Your virus should have a different capsid shape (e.g., icosahedral, helical, complex) than the one above and be non-enveloped.

Part II – How Could a Virus Have Entered?

Terry considered what she had learned so far. “So the Ebola virus could be inside my cells? But how? How exactly could a virus get inside? It seems to start at the plasma membrane... I’d better keep reading.”

In the first step of infection, viral proteins interact specifically with host cells. Different viruses like influenza, rabies and even Ebola each have unique glycoproteins on their surface that bind only to specific receptors on the particular host cells they infect. For example, the influenza virus uses the HA (hemagglutinin) protein for binding to the host cell receptors on respiratory epithelial cells. A rabies virus relies on the G protein protruding out of its viral envelope to attach to the host cell receptors of neurons. Ebola virus uses GP to bind to the host cell receptors on a wide variety of cells, beginning with the macrophages and dendritic cells of the lymphatic system. Once viruses attach to the host cell in this very specific manner, there are three major ways for them to complete the second stage of infection, entry into the host cell. The first is by direct injection of its genome (DNA or RNA) into the host cell at the cell surface. The second is the binding of the virus to the plasma membrane, followed by the fusion of the viral envelope with the host membrane to transfer the viral genome (DNA or RNA) into the host cell. The third way is for the virus to bind to the host cell membrane and become internalized into the host cell via the endocytic pathway.

“This is very strange,” she thought.

Questions

1. Why is viral attachment to the host cell specific between one virus and one type of cell?
2. List several types of host cells and the associated virus that binds to the host cell.
3. What are three major ways in which a virus enters a host cell to deliver its genome?
4. Formulate a hypothesis as to why there is more than one mechanism of viral entry into host cells.

Part III – The Battle between Viruses and Cells

“Now if the virus and its genetic material have gotten inside of my cells, what happens next?” Determined to find out, Terry read further and paraphrased the text.

“The next step is viral synthesis. So, it looks like once the virus enters my cells it hijacks the cell machinery including many of my cells’ enzymes and ribosomes normally used to make my own proteins. The virus does not have these proteins and structures so it relies heavily on the host cell to do the work for it. This process involves not only replication of the genome, but also transcription of viral genes and translation of viral proteins. I remember learning about transcription and translation in biology class. Now this is starting to come together. Still, this really bothers me to think that the Ebola virus could be in my cells doing all this crazy stuff.

“So after viral synthesis comes viral assembly. This step sounds a lot like a factory, because the viral proteins and genomes are put together to make complete viral particles. But then they still have to get out of the cells

“Ah, I see, this step is called viral release and can differ between viruses. Some viruses with envelopes bud from the host cell, taking pieces of the host cell membrane with viral proteins incorporated within, while others leave by exocytosis in vesicles that bud from the endoplasmic reticulum or Golgi. Viruses without envelopes lyse (break open) the host cell and leave that way, often killing the cell in the process.”

“It’s almost like a battle between the virus and my cells. These viruses invade the cell to take over, and the cell doesn’t even know it right away! Then a whole army of new viruses leave the cell and go out to invade and do battle with all my other nearby cells.”

Questions

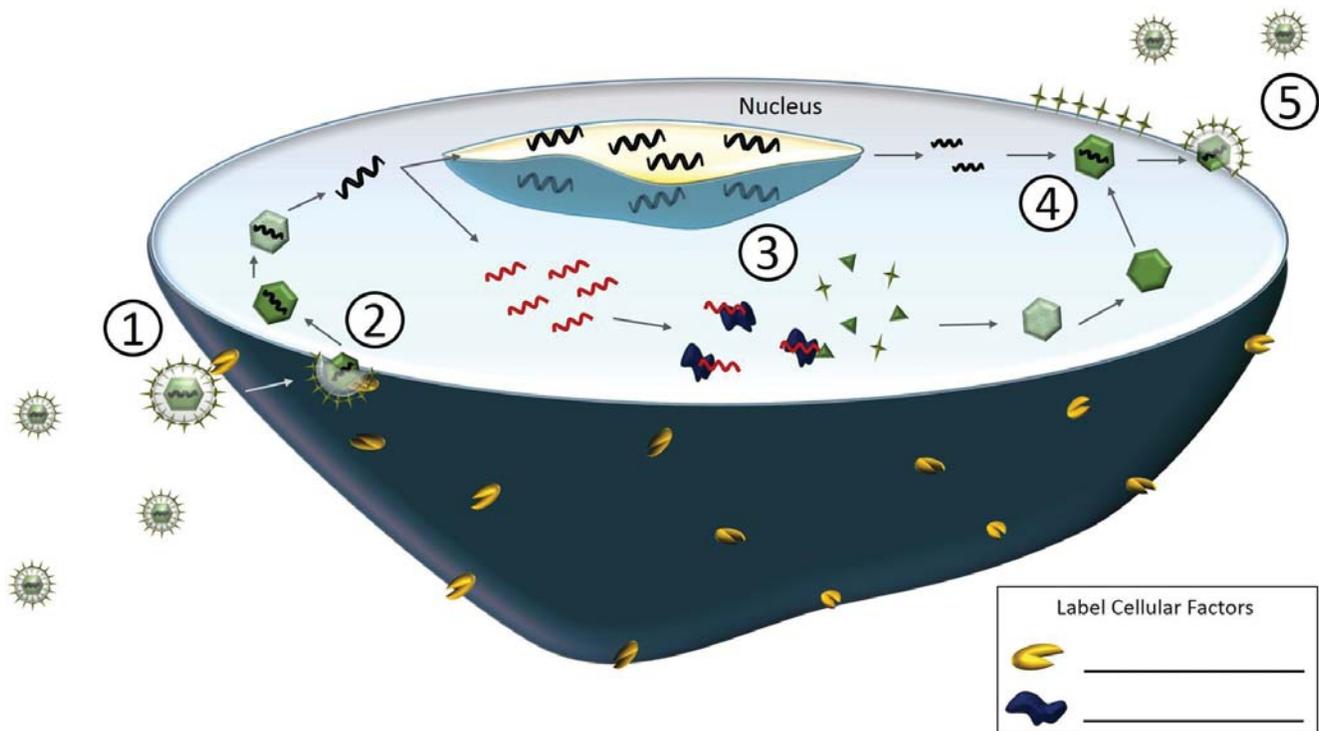
1. Describe the essential cell “machinery” that viruses use to make a new virus.
2. Why do viruses need the machinery to make more viruses? Why can’t they replicate on their own?
3. What are the structures that need to be put together during viral assembly? Consider the key structural components of viruses described earlier.
4. How does the army of new viruses get out of the cell to infect the nearby cells?

5. Examine the diagram below depicting viral infection of a typical cell.
- a. Identify all (five) of the steps used by viruses to get into the cell, make copies of viral proteins and leave the cell as an army of viruses out to attack nearby cells.

- i. _____
- ii. _____
- iii. _____
- iv. _____
- v. _____

- b. Label the two cellular components indicated on the diagram.

Figure 2. Viral infection of a typical cell.

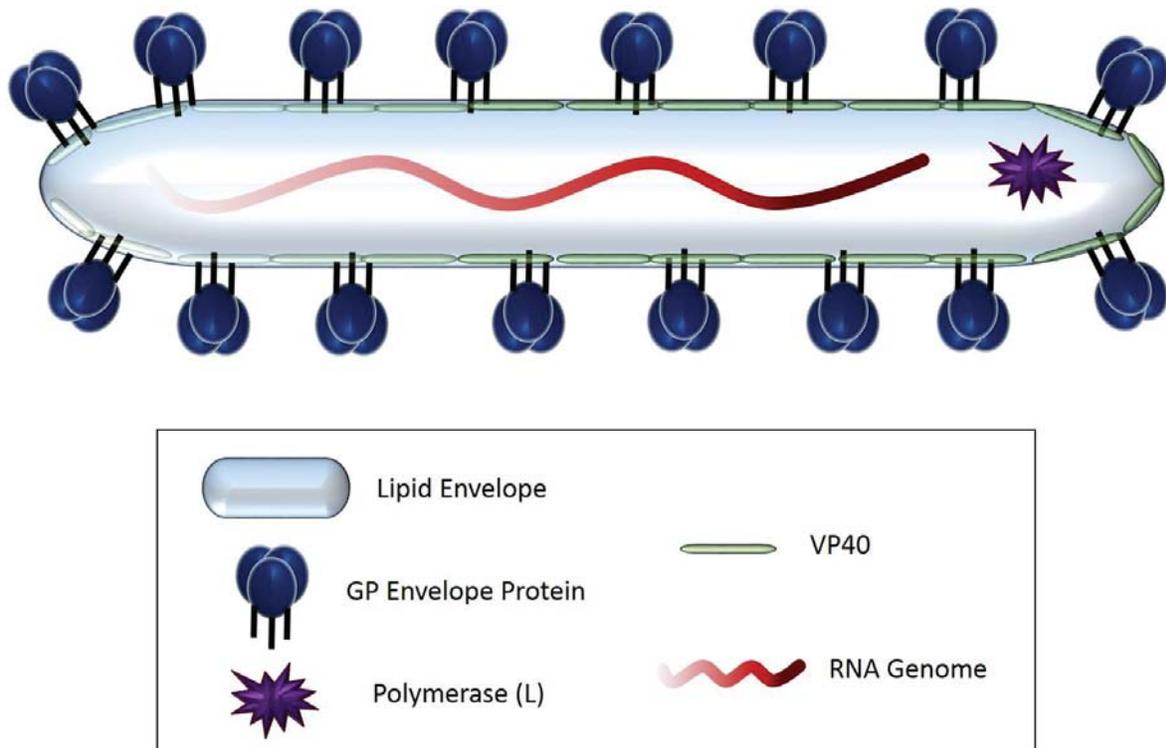


Part IV – The Ebola Wars

In the middle of searching for more information on the Ebola virus, Terry began to feel gravely ill. Feverish, achy, nauseated and weak, Terry’s worst fears came true—the symptoms were consistent with an Ebola virus infection. While she now knew that Ebola virus could not be transmitted through the air, she recalled that during her trip to West Africa she had a small cut on her hand while she was bandaging a patient who had high fever and was hemorrhaging. The exchanged fluid may have contained Ebola virus particles that infected Terry’s cells. After five days of illness including repeated vomiting and extreme pain, Terry wondered if this was the end. A decision was made to transport Terry to a special facility for treatment and isolation.

Ebola is an enveloped, single-stranded RNA virus with a capsid and matrix made of VP40 and other viral proteins. Ebola packages its own RNA-dependent RNA polymerase (L) (see Figure 3). Like many viruses, Ebola goes through

Figure 3. Ebola virus.



the processes of viral attachment, entry, synthesis, assembly and release. Recall that the Ebola virus has the protein GP on its surface, which is required for attachment and entry to the host cell.

Once the virus attaches to the host cell, a series of events through the endocytic pathway leads to its entry into the cell. This means the virus comes into the cell enclosed in a vesicle from the plasma membrane and gets delivered to endosomes. Inside the endosome, the virus relies on the low pH to modify GP and help it fuse with the membrane of the endosome. Once the viral genome is inside the cell cytoplasm, viral synthesis can begin, including genome replication, transcription of viral genes, and translation of viral proteins. The packaged Ebola L enzyme is important for initiating these synthesis steps. One protein produced that is important to the structure of the Ebola virus is called VP40, which determines the filamentous viral shape and interacts with the viral capsid. VP40 is made at the ribosomes of Terry’s infected host cells, along with other Ebola virus proteins like the RNA-dependent RNA polymerase (L) and the envelope glycoprotein (GP). Later, the VP40 proteins assemble with the other viral factors, like the viral genome,

at the cell's plasma membrane and acquire GP proteins that are already inserted in the host cell membrane. At this point, the complete viruses can bud from the cell to spread the infection.

This very battle was occurring between Terry's cells and the Ebola virus.

Questions

1. Examine the diagram (Figure 4, next page) showing the life cycle of the Ebola virus.
 - a. Label the five major steps used by Ebola virus to infect cells. In what specific ways are these similar or different from those you labeled in the general virus life cycle?

i. _____

ii. _____

iii. _____

iv. _____

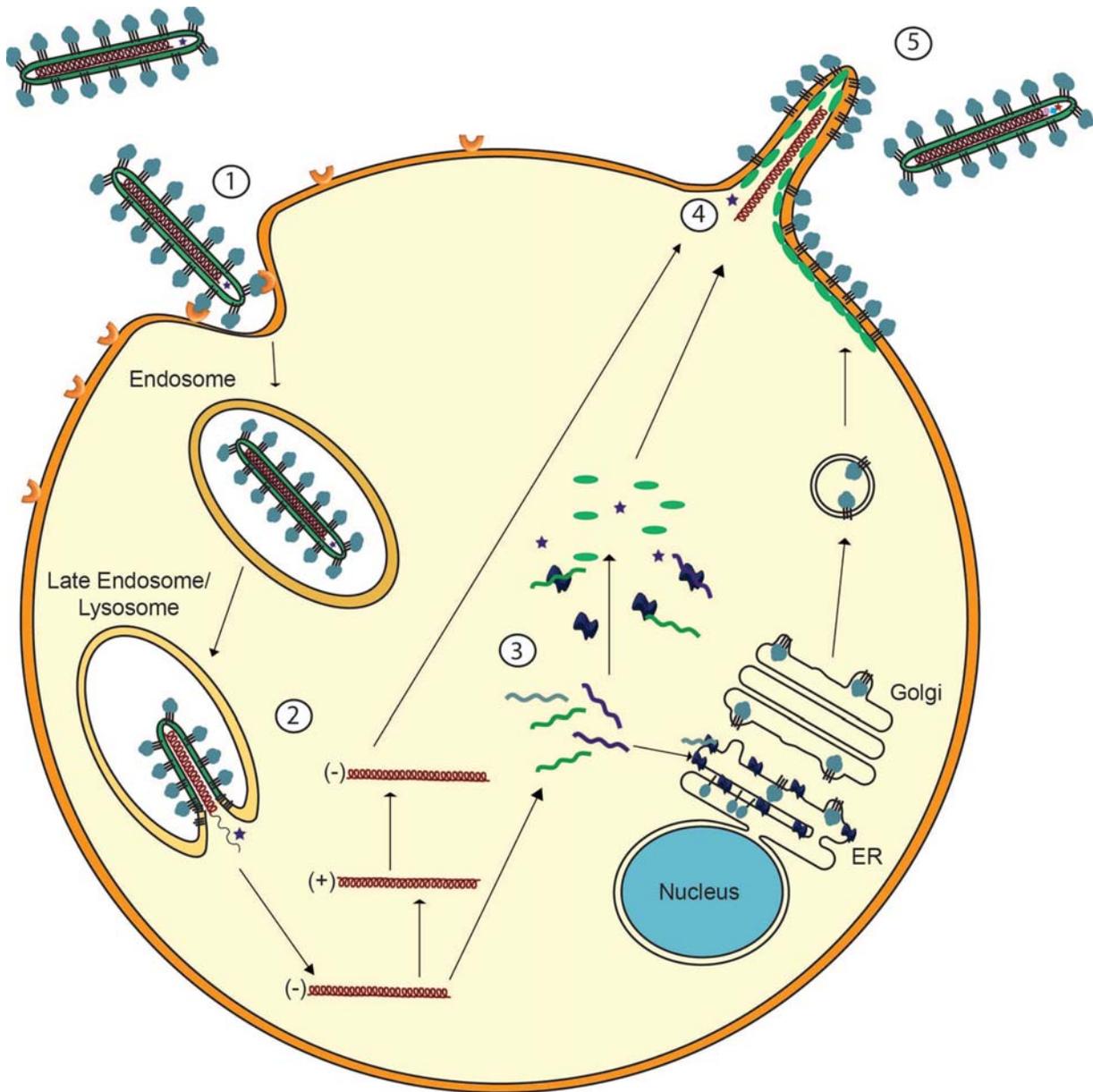
v. _____

Key similarities and differences:

- b. Label the key viral and cellular factors in the indicated areas of the diagram. Describe each of their roles.

2. Formulate a hypothesis as to what would happen to viral replication and budding from the cell if the ribosomes did not make VP40.

3. What is one structural component of the Ebola virus to target for a vaccine that prevents infections like Terry's? Explain your answer. Keep in mind the Ebola virus structures and that vaccines are developed to prevent viral infections (for example, the flu vaccine contains a weakened form of the influenza virus that does not cause disease).



Label the Viral Factors

	_____		_____
	_____		_____
	_____		

Label the Cellular Factors

	_____
	_____

Part V – Treatment

Terry's doctor knew quick action was necessary to help her survive the Ebola infection. The doctor had four options to treat Terry's condition: a vaccine, a standard antiviral medication, an immunotherapy-based method of treatment, and serum from an Ebola patient who had fully recovered.

The first option, a vaccine in clinical trials, could potentially provide protection against a viral infection when used prior to contracting the disease. Vaccines typically introduce the body to an antigen, consisting of the dead virus, or parts of a virus, such as a specific glycoprotein from the viral protein coat/envelope. These non-self antigens are considered foreign to the body and invoke an immune response where antibodies are made against the viral protein in the vaccine. Once antibodies are made and circulated throughout the body, they can attach to the viral antigens and the immune system destroys the antigen. This immune response takes time.

When considering the second option, Terry's doctor thought about antiviral therapies for other viruses, like the flu. She knew that with influenza infection, the antiviral medicine Tamiflu™ was only effective if administered within the first 48 hrs of infection. Unfortunately, Terry was in late stages of the disease, and there were no such approved Ebola-specific antiviral medicines currently available for use.

The third option was immunotherapy with the investigational treatment ZMapp.™ ZMapp is a treatment method that uses three unique antibodies against Ebola GP made in tobacco plants. While there had not been any large-scale human trials at the time of Terry's infection, when these antibodies were injected into Ebola-infected mice and rhesus macaque primates, the animals showed increased survival. As such, ZMapp was thought to be a potentially effective antiviral/immunotherapy-based treatment for Ebola infections in humans, and in a few cases was used to treat human Ebola patients during the 2014 outbreak. Although the mechanism of action for ZMapp had not been elucidated yet, researchers believed that since the antibodies in ZMapp bound to the glycoprotein (antigen) on the Ebola virus, it prevented viral attachment to the cells and thus did not allow entry or viral replication.

A final option would be to give Terry serum from a patient who had recovered from an Ebola infection of the same strain. This serum would be rich with Ebola-specific antibodies to enhance Terry's immune response. However, this method of treatment required identifying an Ebola virus survivor who had blood type compatibility with Terry and who was willing and able to donate serum in a timely fashion.

Question

1. Synthesize the information provided above. Come up with an argument as to the best treatment plan for Terry.

Part VI – Recovery

Terry's symptoms cleared and she was virus free. The battle was now over and Terry's cells won. One would never know whether it was the treatment, Terry's own immune system, or a combination of the two that won the war against Ebola. In the end, Terry survived the potentially-deadly infection and was able to return home without any long-term effects, other than a newfound understanding and appreciation of how viruses, like Ebola, replicate and cause disease.

*Victory at all costs, victory in spite of all terror, victory however long and hard the road may be;
for without victory, there is no survival.*

—Winston Churchill—



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