Antiviral Drugs Targeting Host Proteins an Efficient Strategy

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Keywords: Proteins, Viruses, Drugs

Abstract

Viruses have the ability to spread rapidly because the proteins and enzymes from the host cell help in the development of viruses. Although there are many vaccines that can prevent some viruses from infecting the body, the antiviral drugs today have not been effective in combating viruses from the start of spreading. This is due to the fact that the processes inside a virus are still being studied. However, host proteins proved to be valuable factors responsible for viral replication and spreading. It was found that certain functions such as capsid formation of the virus utilized a biochemical pathway that involved host proteins and some proteins of the host cell were evolutionarily conserved. When the important host proteins were altered, or removed the viruses weren't able to replicate as effectively. It was concluded that targeting the host proteins had a significant effect in viral replication. This approach can stop viral replication from the start, create less viral resistance, and help find new antiviral drugs that work for many different types of viruses. This review will analyze five research articles about protein interactions in viruses and how monitoring the proteins and biochemical pathways can lead to the discovery of druggable targets during development. The purpose of this review is to explore how targeting the factors that enable viruses to spread can allow the discovery of new antiviral drugs.

Introduction

After a virus is able to enter the body, the host cell of the genome is replicated. The two types of viruses are DNA and RNA. Viruses with DNA will use the host cell's proteins and enzymes to create more viral DNA to be made into mRNA (messenger RNA) in order to start protein synthesis while viruses with RNA use the host cell's core proteins in the RNA to create more viral mRNA (Lodish et al., 2000). During the replication process, there are proteins and enzymes that direct each step. Primarily host protein complexes have been an interest in identifying druggable targets because it influences the development. There were studies (Lingappa et al., 2013; Koyuncu et al., 2014; Gang et al., 2006; Reed et al., 2012; Klein et al., 2005) that analyzed protein interactions such as capsid formation, sirtuins, APOBEC3G, RNA helicases and core proteins. The methods that were done were able to determine which protein complexes helped the virus and where to inhibit them during the replication process. For example, when capsids (protein shell that protects viral genome) were studied in viruses there was evidence that the formation had a biochemical pathway that used protein complexes and ATP (Lingappa et al., 2013). Furthermore, in other studies specific proteins such as DDX6 and core proteins were identified to be responsible for the activation of capsid assembly (Reed et al., 2012).Although there are vaccines that help immunity against some viruses it does not help for those who were previously infected. Today's antiviral drugs target the viral proteins instead of host proteins. Targeting the viral proteins can lead to rapid viral resistance against the drug. In some rural areas hospitals are not easily accessible, for instance, RABV (rabies virus) is still a problem because some people are not able to make it to hospitals in time to get the necessary vaccines that stop the virus (Lingappa et al., 2013). Therefore, by targeting the host proteins that are responsible for virus development can lead to the discovery of antiviral drugs that are

inexpensive and effective. By analyzing protein interactions of viruses it can stop the virus from spreading from the start, similar techniques can be applied to a wider range of viruses and new antiviral drugs can be improved that restrict viral resistance. This review will examine the applications that are applied to find druggable targets in protein interactions in viruses.

Stopping Viral Replication from the Start

One of the most important steps for the development of a virus is to replicate its genome. As previously stated, DNA and RNA viruses use the host cell's proteins and enzymes to make multiple copies of its genome. The capsid is an important feature of a virus because it's the barrier that protects the viral genome. In one study (Lingappa et al., 2013) it was discovered that capsid formation was not spontaneous, but there was a biochemical pathway that used host proteins and ATP (adenosine triphosphate, cellular energy). By studying the biochemical pathway five proteins were found to be responsible for capsid formation: N (nucleoprotein), P (phosphoprotein), M (matrix protein), G (glycoprotein) and L (large protein). It was found that proteins N, P, and M had the greatest effect in capsid formation. To inhibit some of the proteins a compound, PAV-866, proved to be effective in stopping capsid formation (Lingappa et al., 2013). The results revealed that it was possible to stop viral replication by targeting the host proteins in the premature stage without harming the host cell. Focusing on the host proteins made a difference because it showed that there were other factors besides viral proteins that could be inhibited successfully. Along the lines of capsid formation, Klein, Dellos, & Lingappa (2005) studied core (structural protein product from the N-terminal) in capsids of HCV (hepatitis C virus). Core is responsible for directing the formation of the envelope (layer that covers the capsid) it can signal lipids and proteins to form around the capsid for another layer of protection. The N-terminal was studied in detail because it had important amino acids that were vital in

capsid formation. It was found that by removing 42 amino acid residues in the N-terminus the effect of capsid assembly was reduced and the core could not direct lipids to form. Unfortunately, the specific residues could not be identified, but the results provided information that can influence further research to find the unknown residues that affect the formation of the envelope. This study could be an alternative if compounds that inhibit the capsid itself cannot be found. As more attention is given to the host proteins that help in viral replication new functions and pathways are being discovered. For both studies, there will need to be further research because the compound, PAV-866, although effective still needs to be tested on animals and monitored for any side effects and the interactions of the core and envelope of the capsid the residues will need to be identified. However, in the long run targeting the host proteins could become effective in finding antiviral drugs that are fast enough to stop replication.

Inhibiting Proteins can be applied to a Wider Range of Viruses

The current antiviral drugs inhibit certain viral proteins and cannot be used in numerous types of viruses. Despite the differences in each virus there has been a conserved factor in the host cell throughout history. Koyuncu et al, (2014) studied sirtuins, proteins that have the ability to conduct metabolic processes. These proteins are able to help with basic cellular functions and have properties that could reduce viral progeny in DNA and RNA viruses (Corda & Di Girolamo, 2003). The researchers inhibited 7 sirtuins in a HCMV (human pathogen human cytomegalovirus) infected cell and the result was that there was an increase in viruses. This meant that without sirtuins viruses could easily replicate, so to see if sirtuins had an effect on DNA and RNA viruses they experimented with a HSV-1 (herpes simplex virus 1, DNA virus) and influenza virus (RNA virus) infected cells. It was found that all the viruses increased, but HCMV and influenza had the largest increase and HSV-1 had a slight increase. Although the

rates of viral development were different the data did show that by inhibiting sirtuins the DNA and RNA virus were able to replicate and infect the cell. Since most cells have sirtuins it could become easier to target and enhance them to combat all types of viruses.To understand more of the history of sirtuins they experimented with E. coli bacterial cells and the protein similar to sirtuin (CobB) and infected the cell with T4 phage. CobB was enhanced and the T4 infection was significantly reduced and slowed down cell lyses. When CobB was inhibited T4 infection increased. It was concluded that CobB was a defense mechanism that had been present in bacteria throughout history and conserved. After experimenting they understood that sirtuins were conserved proteins that had antiviral properties and could be altered to affect a broader range of viral replication. Another evolutionary factor in host cells was also researched. Reed et al., (2012) conducted research on HIV-1 capsid formation and how DDX6 (helicase protein) played a factor in forming the capsid. When capsids are formed in HIV-1, Gag (genetic material that encodes for core proteins) assembles near the cell membrane and is produced in the cytoplasm when bonded with a PB (Processing body, site where RNA goes through translational repression). It was discovered that gRNA (genomic RNA) interacted with Gag first before capsid formation and that lead to the identification of ABCE1 (binding site for ATP). It was concluded that DDX6 and ABCE1 both helped with viral development. Interestingly, ABCE1 is also found in West Nile virus and is one of the important factors in cell replication (Reed et al., 2012). The findings could suggest that there are more relationships in different viruses that still need to be further researched. The way to recognize common factors in viruses is to analyze the host protein functions that aids in a virus.

Development of Antiviral Drugs that inhibit Viral Resistance

The rise in viral resistance is due to the use antiviral drugs targeting viral protein. Current antiviral drugs target the viral proteins because it is released from the virus first in order to control the host cell's functions. This method eliminates replication from the start, but enables the virus to become resistant. It was stated that the antiviral drugs today are restricted in inhibiting different kinds of viruses and that host proteins are better to inhibit because it has been evolutionarily conserved (Koyuncu et al., 2014). This means that the host proteins such as, capsid proteins, have not evolved throughout history and therefore would have less resistance towards antiviral drugs. Furthermore, host proteins like sirtuins can also be enhanced to fight off viral proteins. Enhancing host proteins has been an interest in one study (Gang et al., 2006). The research was focused on APOBEC3G (Apolipoprotein B mRNA-editing enzyme-catalytic polypeptide-like 3G), which is a protein that provides defense against HIV. However, the Vif (viral infectivity factor) of HIV cleaves APOBEC3G and causes it to be ineffective in combating the virus. It was found that there was a host protein factor, IFN-α, in APOBEC3G that could be enhanced to stop Vif from cleaving it. The processes of APOBEC3G were observed and it was possible for the researchers to reverse the process of infection by altering IFN-α. The results could lead to further research in finding hidden host protein factors that could be used to stop multiple types of viruses without having to worry about viral resistance.

Conclusion

In conclusion, today's antiviral drugs are still ineffective in stopping replication of multiple types of viruses. The ongoing research that has been conducted favors targeting host proteins rather than viral proteins. The evidence in each research article proved that the different factors of host proteins can be inhibited or enhanced to reduce infectivity of viruses, but it cannot ultimately be ruled out that it is the most effective way. The research was able to acknowledge an

alternative way in producing new antiviral drugs; there will need to be further research to test out potential compounds and they would need to study the long-term effects of the virus and monitor any resistance. The evidence from the research proved that targeting the host proteins would be beneficial in stopping viral replication from the start, applying similar targeting techniques to a wide range of viruses and creating less resistance compared to viral proteins. The most significant point after analyzing the evidence was that the interactions in the cell and virus are still unknown and there could be alternative possibilities to fight viruses.

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