Structural Challenges Posed by gp120 in the Development of an Effective HIV Vaccine

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Abstract

HIV affects over 38 million people worldwide, yet an effective vaccine has not been developed, partly due to the virus's high mutation rate and other challenges. The HIV envelope glycoprotein is the only viral receptor found on the surface of HIV and is responsible for facilitating entry into host cells. Therefore, it is the primary target for neutralizing antibodies and vaccine design. However, the envelope glycoprotein has a high mutation rate, a dense glycan shield, and a low protein density on the virus surface, which has made vaccine development challenging. In addition, HIV has many clinical implications, a major one being HIV-associated neurocognitive disorder (HAND). This literature review examines the role of the HIV envelope structure and function, highlighting how these features hinder immune recognition by neutralizing antibodies and complicate vaccine development, as well as the progression of HAND. By analyzing these obstacles, this research aims to foster a deeper understanding of the challenges and efforts involved in developing vaccines against rapidly mutating viruses, like HIV. This review also highlights emerging strategies–broadly neutralizing antibodies, structure-based immunogen design, and mRNA vaccine technology–that offer hope towards overcoming these challenges.

Introduction

Human Immunodeficiency Virus (HIV) is a retrovirus with an estimated prevalence of infection of around 38 million people worldwide.[1] As HIV attacks the immune cells in a person's body, their immune system slowly loses the ability to defend itself against common illnesses and other infections. If left untreated, HIV can lead to Acquired Immunodeficiency Syndrome (AIDS), the most advanced stage of the infection, where the immune system is severely damaged to the point that even minor infections can become life-threatening.[2]

Because of the danger that HIV presents, developing an effective HIV vaccine is crucial. As a result, various potential vaccines have been tested for more than 35 years.[3] However, an effective vaccine has yet to be developed, due to the inherent structural challenges that HIV poses. Although there exist medications, primarily antiretroviral therapy (ART), they are only effective at suppressing HIV and have several limitations. For example, in some cases, a patient has to take ART every single day to suppress the virus, creating a dependence on the medication. This could create side effects, and still doesn't protect against HIV-associated neurocognitive disorder (HAND).[4] [5] Thus, a preventative vaccine would be the only solution to eradicate HIV and the harmful impacts of HIV infection.

The primary target of vaccines is the HIV surface protein called the envelope (Env) glycoprotein, which is the sole viral protein on HIV's surface. Env is a trimeric protein with three copies of glycoprotein 120 (gp120) and three copies of gp41 that form a mushroom shape, with gp120 composing the head of the mushroom and gp41 composing the stalk portion.[6] While Env

is the primary target for vaccines, it poses significant challenges for vaccine design. These challenges include the low copy number of Env on the surface of HIV virions, the high glycosylation density of gp120 that forms a shield that protects it from the immune system, and most importantly, the high variability and mutation rate of gp120.[7]

This literature review provides an overview of HIV, with a focus on the gp120 glycoprotein. It highlights its structural features, including the low copy density, the glycan shield, and its high mutation rate, which challenge the development of a vaccine, and possible solutions to the vaccine problem. In addition, this review highlights the damaging effects of HIV infection that are prevalent due to the lack of an effective vaccine. This includes how prolonged infection impacts core biological functions in organs such as the brain, which has been linked to HAND. Guided by the question, “How does the HIV gp120 glycoprotein challenge the development of an effective HIV vaccine?”, this research paper aims to explain the challenges in vaccine development.

Overview of HIV and the HIV Env glycoprotein

HIV is a retrovirus, which means that it uses RNA as its genetic material, which is then converted into DNA once it enters the host cell. RNA is converted into DNA through an enzyme called reverse transcriptase, which enables the viral DNA to get integrated with the host’s DNA. Once integrated, the virus hijacks the host’s machinery and reads the viral DNA, which produces viral proteins that go on to form new viruses that infect more cells. Due to the virus being integrated with the host cell, it is impossible to eliminate it, as it could lie dormant and reactivate at a later date, a concept known as latency.[8]

HIV has a singular type of surface protein known as the Env glycoprotein. The Env is trimeric and is comprised of two main parts, gp41 and gp120, that form heterodimers (Figure 1). Once assembled, gp120 forms the top of the protein, and gp41 forms the stalk that is proximal to the viral membrane. A primary focus of this paper will be on gp120, as it is essential to understanding the HIV lifecycle and is a viable target for vaccine development. The gp120 glycoprotein’s main purpose is to bind to the host CD4 receptor, which is the first crucial step needed to enter host immune cells. Once bound, gp120 undergoes a conformational change, as gp120 usually exists in a form where it hides its co-receptor binding site. Once it changes, gp120 unmasks its binding site and binds to the host cell’s co-receptor (CCR5 or CXCR4), which allows gp41 to insert itself into the host membrane. Once inserted, the virus and host membranes fuse, allowing the viral RNA to enter the host cell.[9] Once inside, the virus begins making copies of itself.

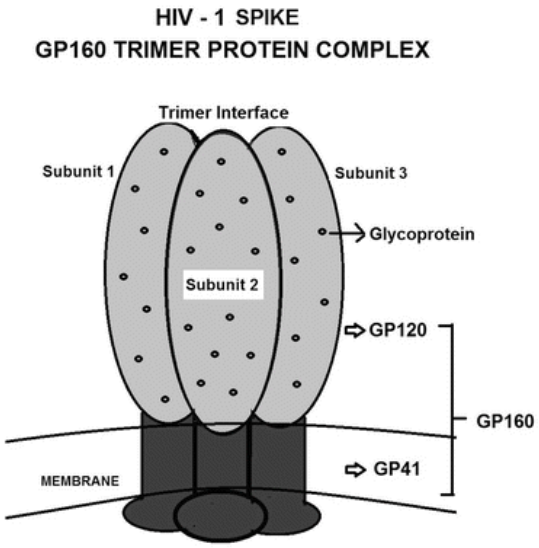

Figure 1. Structure of the HIV viral envelope showing the envelope glycoproteins gp120 and gp41. gp120 facilitates viral attachment to host CD4 receptors, and gp41 allows the virus to fuse with the host membrane. These proteins are key targets for vaccine research but are difficult to neutralize due to their structure. Reprinted from Nilofer, et al.[10]

gp120 variability: Mutation rates and conserved regions

One of the biggest challenges when creating an HIV vaccine is its high mutation rate. Since HIV is a retrovirus, it uses an enzyme called reverse transcriptase, which converts its RNA to DNA, to integrate with the host cell. However, reverse transcriptase lacks the ability to proofread, which means that mutations in the DNA will go unchecked, leading to gp120 having a rapid and frequent mutation rate, with 1 out of every 2-3 virions being a mutant, making its mutation rate roughly 10-100 times higher than that of influenza.[11] [12] This poses a problem for a potential vaccine, as it would be challenging to create a vaccine that targets multiple strains, and not just one specific mutant.

Currently, the best solution to this problem is an approach known as broadly neutralizing antibodies (bNAbs). Antibodies are proteins that the body uses to counteract and neutralize foreign substances, known as antigens. One can think of bNAbs as arms that hold an antigen in place, preventing further movement and restricting their ability to infect cells. bNAbs are a very rare form of antibody, and can naturally occur in HIV-infected individuals, usually people who have been infected for 10+ years. They possess rare structural features that enable them to bind to key points on gp120, known as conserved regions. Conserved regions are parts of an Env that remain largely unchanged across different strains because they are essential to the life cycle of HIV, and any mutations in those regions could hinder HIV's ability to infect. Some of the main conserved epitopes on gp120 include the CD4 binding site, the V3 glycan region, and the

gp120–gp41 interface areas (Figure 2). By focusing on these conserved regions, bNAbs have a more consistent and general target to neutralize, which, in theory, should solve the mutation problem.[13] However, as of now, there has been no successful HIV vaccine strategy that results in the production of bNAbs in humans.

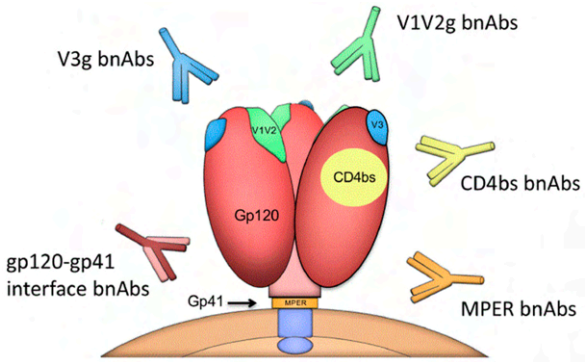

Figure 2. Major conserved regions on the HIV Env spike targeted by bNAbs. The labeled sites: CD4 binding site (CD4bs), V1/V2 glycan region (V1V2g), V3 glycan region (V3g), gp120–gp41 interface, and the membrane-proximal external region (MPER). These regions are the main focus of current vaccine efforts. Reprinted from Stefic, et al. [14]

Structural challenges: gp120's glycan shield and low density on HIV virions

Another challenge in developing an effective vaccine is the glycan shield of gp120. Env is covered with host-derived sugar-based glycan forms. In fact, approximately 50% of the Env molecular weight is these N-linked glycans, which are sugar chains attached to asparagine residues. Broadly, Env uses the host cell's self-produced sugars to protect and disguise itself. Think of it as a spy wearing different clothes to blend in with their surroundings. Due to being covered in sugar produced using host machinery, the body recognizes the glycan-covered Env as "self," and therefore, the immune system will not try to neutralize HIV. This is also known as immune escape.[15] Along with physically blocking antibodies, in the event an antibody catches, the glycan shield is dynamic and can shift itself to escape the antibody pressure. The current solution to this problem once again relies on bNAbs, but without success in humans.[16]

Finally, there are very few gp120 proteins expressed on the surface of HIV virions, with approximately 10-14 Env trimers on their surface.[17] For reference, influenza has approximately 450 spikes, which makes HIV's spike density one of the lowest among enveloped viruses. With this low Env spike density, antibodies face difficulties in cross-linking, which reduces effective binding. Antibodies have two arms that enable them to bind to two gp120 molecules, crosslinking them, which promotes stronger binding and neutralization of the virus.[18]

Currently, one of the most promising therapeutic solutions to overcome HIV's rapid mutation is the development of bispecific and trispecific antibodies. Bispecific antibodies can bind to two different epitopes simultaneously, while trispecific antibodies can target three epitopes on the same Env. An epitope is a specific part of an antigen to which an antibody binds. These epitopes are usually conserved regions of the Env spike, such as the CD4 binding site. With bi- and tri-specific antibodies, these antibodies can lock onto two or three specific parts of the Env spike, without needing to target multiple spikes. These types of antibodies are currently being evaluated for clinical efficacy.[19]

Clinical implications of HIV infection: HIV-associated neurocognitive disorder

Beyond vaccine development, these challenges have severe clinical implications. In the absence of a vaccine, patients remain susceptible to HIV-related complications and infections. One of the most overlooked aspects of HIV is HIV-associated neurocognitive disorder, also known as HAND. HAND is a spectrum of cognitive, motor, and behavioral impairments that are caused by HIV infection. Impairments can range from major depression to coordination difficulty or dementia. Some form of HAND affects over half of all HIV-infected individuals, but HAND remains relatively unknown, even among individuals infected with HIV.[20] On a high level, HIV produces a protein called Tat, which travels in the bloodstream until it reaches the brain, where it then disrupts the blood-brain barrier. Once in the brain, Tat can directly damage and kill neurons, inflame the central nervous system, and disrupt dopamine signaling.[21] Even with antiretroviral therapy, which controls HIV within the body, it doesn't control HIV in the brain. This is because ART simply turns off viral replication, but doesn't eliminate the proteins already produced, such as Tat. However, ART does lower the incidence of severe impairments, but it still does not reduce the incidence of HAND in general. The only solution to prevent HAND is to create an effective HIV vaccine.[22]

Conclusion

Due to HIV's high mutation rate, glycan shield, and low spike Env density, an effective vaccine has been and will continue to be a challenge for researchers. Currently, the best solutions lie in bNAbs and bi- or tri-specific antibodies, which are still in development. Other solutions include structure-based immunogen design, where the immunogens model the structure of an HIV Env trimer. By presenting the immune system with a model of the Env trimer, scientists hope to elicit antibodies to neutralize the virus. Another promising approach is mRNA vaccines, which can instruct the body on how to create the HIV spikes themselves. This allows the body to "practice" against a model HIV, training the body to recognize and respond to it. Both of these solutions act as a form of training to the immune system, so HIV would be more easily identified and easier to target. [23] [24] While some HIV scientists claim that a vaccine is essentially impossible due to the extreme difficulties that HIV poses, the promising innovations

highlighted here provide hope for the development of an effective vaccine that would not only eradicate HIV and HIV-associated complications, including HAND.

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