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Analysis of the effect on immune recognition of the glycosylation of viral envelope based on the analysis of the HIV-1 envelope

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Abstract:
This passage firstly presents the global overview of the Human immunodeficiency virus (HIV), then providing a comprehensive review of the difficulties in the development of vaccines against the HIV, focusing on glycosylation modification of the envelope protein. During the infection process of this virus, the glycosylation modification help the virus evade the monitoring of the immune system through a series of immune evasion mechanisms. The glycosylation modifications of the virus are mainly located on the envelope of the virus. During the formation process of the envelope, the core products Group-specific antigen exerts a vital influence and shows positive effects in the maturation of the surface envelope proteins. Also, the components of the viral envelope and the mechanisms of glycosylation are introduced. The envelope protein have a significant impact in the immune evasion. Also, the passage introduces the recent progress in the research on treatment for the virus. An overall review on the impact of glycosylation modifications on immune evasion mechanism of HIV-1 virus is helpful for the future research in this field.

Keywords: HIV-1 virus; glycosylation; immune recognition; Env; gp120 protein.

1. Introduction

The Human immunodeficiency virus has caused a serious public safety and health issues around the world. The virus has resulted in the death of over 40 million people in all regions of the world. This virus induces the human immunodeficiency syndrome by weakening the immune system, finally causing various complications and leading to death. There is not cure available currently. The only treatment method involves using antiretroviral drugs to interfere with transcription process of the virus within the body, thereby reducing the amount of the virus present. The most important obstacles during the research and development process are the complex immune evasion mechanism and the high variability of the virus itself. For the high variability of the HIV virus, it mainly refers to the variation caused by base mutations during the reverse transcription process. Also, the genetic recombination that occurs in two or more viruses to form the various virus populations is one significant factor. In addition, one major challenge is the complex immune evasion mechanisms. The virus can enter dormant memory cells to form latent infection reservoirs. One vital difficulty is the glycosylation of the envelope protein. The surface glycosylation can form a protective sugar shield, covering the recognition sites and creating a physical barrier. The conformational transformation of the active sites caused by the glycosylation is also a important challenge. The immune decoys formed by the glycosylation of the non-structural protein induces many problems, too. For the immune evasion mechanism of the HIV -1 virus, the glycosylation of the envelope protein serves as a linchpin. The analysis of the mechanism of immune evasion mediated by the glycosylation of the envelope of HIV-1 virus may provide ideas for future therapies aimed at identifying pathogens. Additionally, this article reviews the progress made in treatments targeting at glycosylation. The combination of the clustered regularly interspaced palindromic repeat (CRISPR)/ CRIPSR-associated protein 9 (Cas9) gene editing system and the broadly neutralizing antibodies treatment brings hope to the development of healing methods. The newly developed antiretroviral drugs also provided new ideas for targeting active sites in drug research.

2. The formation of the viral envelope

2.1 The synthesis process of the viral envelope

The components of animal viruses usually comprise of genetic materials like Deoxyribo Nucleic Acid (DNA) or Ribonucleic Acid (RNA),the capsid protein [1]. Some viruses are enveloped by a lipid bilayer membranes with glycoproteins, which is defined as enveloped viruses. Discussions of formation of the viral envelopes always began with the creation of virus particle assembly. The process of viral assembly governs all the subsequent stages in viral activities, such as the envelope structure formation.

As a typical retrovirus with envelope structure, the HIV-1 envelope structure briefly illustrates the interaction between the viral envelope structure and host cells. To introduce the formation process of the HIV-1envelope structure, the assembly of HIV-1 virus particles should be introduced at first at Figure 1.

A huge amount of RNA products were produced from the transcription of the HIV-1 RNA on the free cytosolic ribosomes. The core products Group-specific antigen (Gag) and Gag-Pol are just produced from this process. First of all, the Gag is translated as the Pr55Gag, which is a precursor polyprotein. And the Gag-Pol is produced through ribosomal frameshift event in translation, occurring at about 5% relative to Pr55Gag. The complex that mainly composes of Gag protein and RNA is recruited to the plasma membrane, then the complex interact with the lipid microdomains on the plasma membrane, inducing the bending of the membrane and formation of membrane budding. After the formation of HIV conically shaped mature core, the maturation event occurs with budding at the same time [1]. While the infectious viral particles at the mature stage finish the whole budding phase, the viral capsid would be directly enveloped by some lipid membrane taken from the host cells. And for the enveloped protein of the HIV-1 particles, the next part would talk about it.

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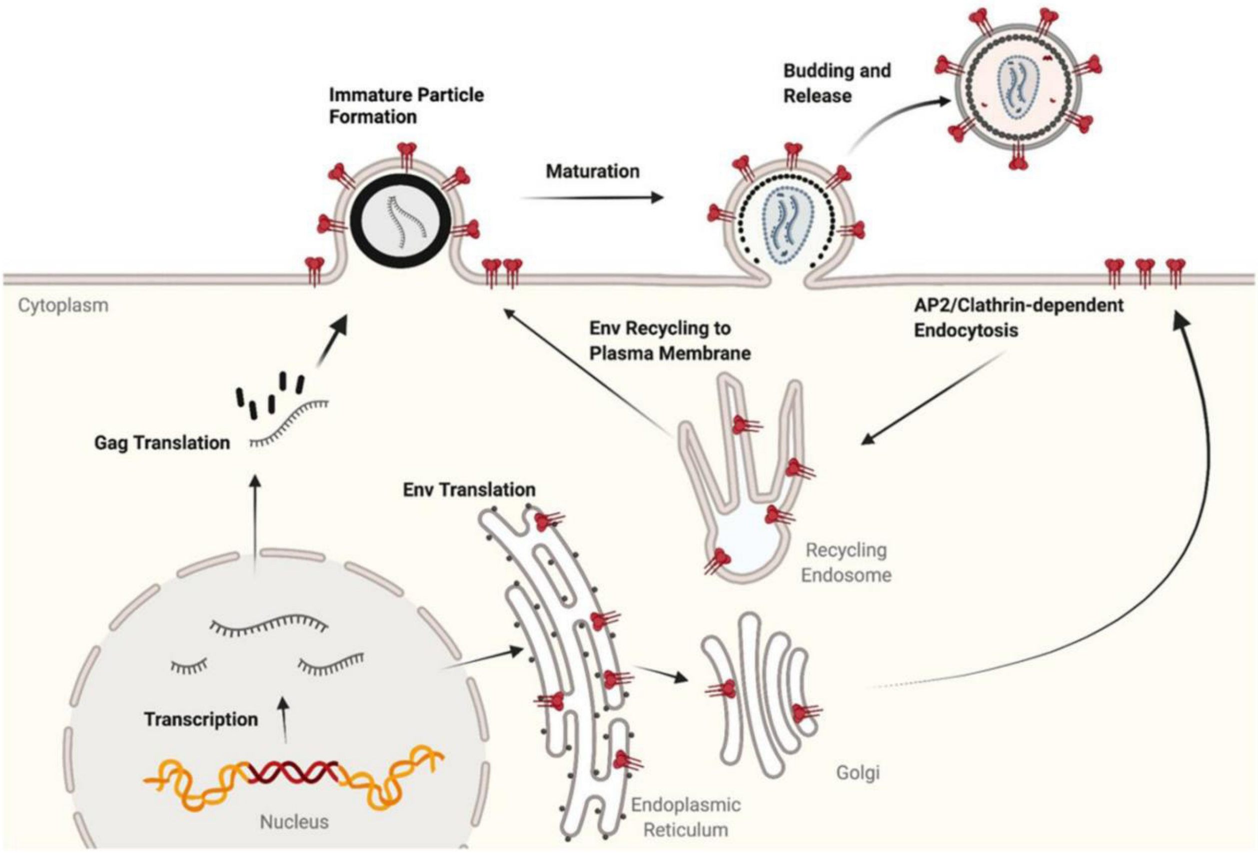

Fig. 1 The assembly process of the HIV-1 virus particles [1]

2.2 Components of the viral envelope

After the brief introduction of the formation of the envelope, it's known that the most components of the HIV-1 envelope are from the lipid membrane of the host cells, including the lipid membrane and some enveloped proteins. They are all taken by the process of the budding and maturation.

Besides some proteins from the host cells, there are also envelope proteins encoded and translated by the virus genetic materials. As for the HIV-1 virus, the self-encoded protein is only Env trimeric protein, which is made up of the trimers of gp120 proteins and gp41 proteins.

For the core protein Gag, it is mainly composed of four functional domains and two linker peptides, which are matrix protein (MA), p6, capsid protein (CA) and nucleocapsid protein (NC) domains. The MA domain functions to promote the merging of the viral core and the host cell. And the p6 domain mainly recruits some functional proteins like endosomal sorting complexes required for transport (ESCRT) protein TSG101 and ALG-2-interacting protein X (ALIX) to promote the membrane fission. The above two structural domains are closely related to the formation of the HIV-1 viral envelope. The CA domain mainly guides the assembly and maturation of the capsid, while the NC domain is responsible for binding to the RNA genome.

3. The relationship between glycosylation and recognition of immune system

3.1 Introduce to the glycosylation

Protein post-translational modification is an essential biological event that profoundly affects on protein function. Among the more than 300 PTMs, the glycosylation is the most diverse and important type. The initiation of glycosylation mainly involves transferring glycans from endoplasmic reticulum to Golgi apparatus [2]. During the process it would add a large amount of glycans and be catalysed by diverse glycosyltransferases and glycosidases to stimulate the maturation of the glycans.

There are multiple forms of glycosylation existing in human physiology, the N-glycosylation, O-glycosylation, etc. And the N-glycosylation is the dominant type in the viral glycosylation modification, especially for HIV-1 virus particles.

The formation of N-glycosylation is related to the binding of oligosaccharide GlcNAc and residues of the protein aspartate [2]. Three subtypes of N-glycan are produced in this process. They can be divided as complex, hybrid and high mannose polysaccharides by their branching of the side chains. All the N-glycans have one common core structure, the core pentasaccharides. The core structure ensures the relative stability of the N-glycan structure. The glycan residues that links to the side chains extended the structures and functions.

Usually the glycosylation is important to numerous functional activities in human body. It basically can be seen as one key regulatory factor in many physiological process, such as the immune recognition, the signal transduction, etc. Furthermore, it deeply involves the regulatory process of the production, folding and modification of the protein.

However, aberrant glycosylation is also associated with various health problems. As one essential biomolecules within human physiology, the abnormal glycoprotein modification is widely connected with various diseases. Although the viral protein glycosylation can not be defined as the abnormal glycosylation in human body, the ability of virus to evade the immune system through viral glycosylation modification is related to a lot of health issues.

3.2 The influence of viral glycosylation on immune response

The glycans are usually significant active sites for recognition of immune system. It's widely believed that the modified glycans induce the immune evasion of the virus through blocking antigenic active sites. Through hijacking the N-glycosylation modification mechanism of the host cell and using the glycans from host cells as materials, The active sites on the surface of enveloped viruses undergo molecular simulation and conformational conversion, which prevent the viruses evade the immune recognition.

Otherwise, the microscopic heterogeneity of the viral N-glycosylation also correlates with the immune recognition. After hijacking the glycosylation mechanism of the host cells, some categories of viruses do not follow the classic pathway of glycoprotein secretion, but only secreting as high mannose type directly. The research found the degree of glycan modification of the area with high density of glycans is usually limited [3]. Comparing with the complex type, the structure and the active sites have the microscopic heterogeneity, causing the difficulties of being recognized by the immune system.

Apart from the glycosylation of some structural proteins, some non-structural and secretory proteins can produce the immune decoys by glycosylation. After hijacking the glycosylation system of host cells, some secretory proteins can be glycosylated and secreted outside the cell. While the immune response occurs, the decoy can combine with the antibodies to reduce the strength of the immune response.

4. The glycosylation research of the HIV-1 viral envelope

4.1 The glycosylation pattern of the HIV-1 envelope

As a typical enveloped virus, the HIV-1 Env protein is the only specific antigen that expressed on the exterior of the viral particles and the host cells after infection. Thus making it the main target for host cells to recognize and initiate the immune response. Also, the enveloped protein can regulate the entry of the virus and escape the immune response through numerous mechanisms like the glycan shielding [4].

The mature envelope protein of HIV-1 comprises three gp120 subunits in association with three gp41 subunits. Firstly the precursor gp160 is generated in the rough endoplasmic reticulum. During the process it's folded, trimerized and glycosylated. Then in the Golgi apparatus the precursor is split by the furin-like proteases to form the gp120 and gp41 trimers [4]. The bundles of trimers are binding with the non-covalent way. As a transmembrane domain, the conserved structure and the tight coupling against the gp120 makes the gp41 be safe from the surveillance of the immune system. In contrast, the gp120 is mainly situated on the exterior of the viral membrane. As one of the protein with the highest extent of glycosylation, the structure of the gp120 includes the receptors and co-receptor active sites. After binding with the CD4 receptor, it will go through the conformational transformation, which can expose the co-receptor binding sites to assist with the viral-host membrane fusion [5]. This also proves the significance of the Env for both the immune evasion mechanism and the membrane fusion involving viruses with host cells.

The N-linked glycosylation of the HIV-1 Env is usually seen as the most important type for normal functions of the protein by affecting the folding of the protein. Also, the N-linked glycans may have a influence on the neutralizing antibody response of the HIV-1 virus [6]. Besides the mechanisms like the conformational transformation of the active sites and the glycans shielding formed by the glycosylated polysaccharides. Also, one key mechanism for the HIV-1 glycosylated Env domain to escape the immune response is the immune decoys. Some viruses like lassa virus can drop its glycoprotein subunit as the immune decoys to disturb the immune recognition. The HIV-1 virus can also drop the gp120 domains from the Env to interrupt the immune response [7].

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4.2 The current research progress on glycosylation-based treatment methods for HIV-1

At present, the most common treatment for HIV-1 is the daily antiretroviral therapy, which can decrease the level of the plasma viral load to the level that can not be detected. At the same time, the treatment can limit the potential for spreading. However, this therapy can not eliminate the HIV-1 viruses in the body.

The HIV-1 broadly neutralizing antibodies (bNAbs) can render the virus non-infectious and inhibit infection of the host cells. Many types of passive transfer has already been proved to be useful for protecting human from being infected. However, the immunogens that are able to elicit the bNAbs do not exist yet. Although much research effort has been put, the way to elicit the bNAbs by vaccination is still not found yet [8].

Some researches combine the bNAbs with the CRISPR/Cas9 gene editing system to make a Chinese hamster ovary (CHO) cell system. It's known that some broadly neutralizing monoclonal antibodies (bN-mAbs) need the mannose-5 or mannose-9 to bind with the key sites of gp120 for neutralizing.

The edited gene MGAT1 encodes N-acetylglucosamine transferase I. This enzyme adds an N-acetylglucosamine to the ER to the Golgi apparatus, enabling the N-linked glycan to connect more types of monosaccharides and form complex polysaccharides that contains sialic acid. This cell system can limit the polysaccharide process to improve the immune recognition to prevent the infection of HIV [9].

4.3 The current difficulties and the future prospects

The obstacles the researches meet is still the recognition of the antigen active sites for the viruses and infected cells. The complicated immune evasion mechanisms of the HIV-1 is still the most essential problem for the research to address. Also, as one typical RNA retrovirus, the high variability of the HIV-1 itself is also one hard problem. The CRISPR/Cas9 system also need to be careful about the off-target effects of gene editing.

Recently, one important process has been achieved for the therapeutic strategies for HIV-1 infection. It's not the same as normal ways to target at the Env protein but to target at the capsid protein. The new developed drug Lenacapavir (LEN) can stop the entry and replicating of the virus. As one kind of ART, it can perform a long-acting effect for couple of months. This new drug provided a new approach to treat the infection of the HIV-1 [10].

5. Conclusion

Although currently the identification of the surface active sites of the HIV-1 virus has not been stably achieved, there are continuous breakthroughs in this area. It's currently widely believed that the glycosylation of the Env of the HIV-1 virus plays a role in the immune evasion mechanism. The numerous types of glycosylation also encountered many obstacles in the research process. However, the application of new genetic editing system CRISPR/Cas 9 and the transformation of the idea of identifying active sites are also bringing hope to the current dilemma. The new research findings Lenacapavir also greatly improves the effectiveness of treatment. In the future, the cure for the virus will eventually appear.

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