Structural attributes and binding role of HIV-1 exterior envelope gp120

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Glycoprotein 120 (gp120) plays pivotal role in HIV-1 entry into the host cells, resulting from interaction of gp120 highly conservative CD4 binding site and CD4 receptor on the surface of CD^{4+} T cells. Therefore, gp120 became a major target in development of vaccines for HIV-1 management, based on competitive neutralization of gp120, disabling entry into the host cell. Present study describes the structure of HIV-1 virion and its pivotal protein - gp120, together with mechanism of viral entry through interaction between gp120 CD4 binding site and CD4 receptor. Finally, basic antibodies, suitable for HIV-1 vaccination are commented, with focus on RV144 or the Thai trial (ongoing clinical trial, phase III).

Keywords: CD4-binding site; glycoprotein; HIV envelope; virus entry; T-cells

1.Introduction

HIV/AIDS is a global deadly disease. Since its discovery in 1983, the Human Immunodeficiency Virus has sustained one of the major pandemics in the history of mankind [1]. Human immunodeficiency virus type 1 (HIV-1) is characterized by extensive genetic variability, as a consequence of high replication and mutation rates and frequent recombination [2,3]. The most up-to-date estimates that more than 30 million people are now living with HIV-1 infection, most of them in sub-Saharan Africa [4]. The virus depends on the physiological state of its target cells for efficient replication, and, in turn, viral infection perturbs the cellular state significantly.

A cure for HIV is still urgently needed and has become a global research priority. A unique cohort of HIV-infected individuals who spontaneously control HIV exists, and these are known as ‚elite controllers' [5]. These subjects represent a model with long term control of viral replication and HIV remission, based on natural $CD4^+$T cells depletion.

$CD4^+$ T cells play important role particularly in the adaptive immune system by releasing T cell cytokines, thus helping to suppress or regulate immune responses [6]. CD^{4+} T cells are a primary target of HIV viral entry, because of interaction between HIV exterior envelope glycoprotein 120 (gp120) and CD4 receptor found on the surface of $CD4^+$ T cells [7,8]. Thereof, perfect understanding of interaction between gp120 and CD4 receptors could lead to development of novel chemical substances with ability to block this interaction and inhibit the viral entry into the host cells.

The present paper focuses on description of role of gp120 in entry into the host cells through interaction with their CD4 receptors and further summarizes recent knowledge in development of HIV vaccines based on interaction with gp120.

2. Structure of HIV-1 virion

HIV is a member of the lentivirus genus, which includes retroviruses that possess complex genomes and exhibit cone-shaped capsid core particles around 120 nm in diameter. Like all

retroviruses, HIV's genome is encoded by RNA, which is reverse-transcribed to viral DNA by the viral reverse transcriptase (RT) upon entering a new host cell [9].

HIV is enveloped by a lipid bilayer, derived from the membrane of the host cell. Lipid bilayer possesses fundamental surface structures - surface gp120, which are anchored to a virus via interactions with the transmembrane gp41 [10,11] (schematic structure of HIV-1 virion is depicted in Fig. 1). Gp120 possesses a high level of glycosylation, which together with the presence of surface-exposed variable loops and conformational flexibility may reflect evolved viral defense against the host humoral immune response [12,13]. Elements of gp120, which are relatively conservative fold into a core, which has been crystallized in a complex with the two amino-terminal domains (D1D2) of CD4 and the antigen binding fragment (Fab) of the human neutralizing antibody, 17b [12]. The gp120 core is composed of inner and outer domains, which reflects the likely orientation of gp120 in the assembled trimer, and a bridging sheet. Components of both domains and the bridging sheet contribute to CD4 binding [14]. The lipid bilayer of virion further contains several cellular membrane proteins derived from the host cell, including major histocompatibility antigens, actin and ubiquitin [15]. Inner surface and a conical capsid core of the viral particle are covered by a matrix shell (p17, app. 2000 copies of the matrix protein) and the capsid protein (p 24, app. 2000 copies) [16]. Inside the conical capsid core, two copies of the unspliced viral genome are encapsulated in nucleocapsid (p7), stabilized as a ribonucleoprotein complex together with three fundamental virally encoded enzymes: protease (p11), reverse transcriptase (p66) and integrase (p31). Furthermore, virus particle contains additional accessory proteins Nef, Vif and Vpr [17].

3. Interaction providing host cell entry

Productive HIV-1 infection depends on host machinery, including a broad array of cellular proteins [19]. The current dogma is that the major HIV reservoir originates from activated CD4+ T cells that have been infected and survive while reverting to a resting state, thereby becoming a memory cell [20]. HIV-1 entry is based on the sequential interactions with the CD4 receptors on the CD4+ T cells and proteins from the chemokine receptor family [21]. The entry of HIV-1 into cell is mainly mediated by the viral envelope glycoproteins (gps) [13], which are synthesized as an ~850- amino acid precursors. After trimerization and posttranslational modification by carbohydrate, 160-kDa glycoprotein (gp160) is formed. Subsequent proteolysis of gp160, carried out in the Golgi apparatus, provides a transformation to gp120 exterior envelope glycoprotein containing relatively conserved CD4 binding site and gp41 trans-membrane envelope glycoprotein [10,11,22,23]. In the mature HIV-1 envelope glycoprotein trimer, the three gp120 subunits are non-covalently bound to three membrane-anchored gp41 subunits. For entry of HIV-1 into a host cell, the gp120 subunit associates with the CD4 receptor and the CCR5 coreceptor and this induces series of

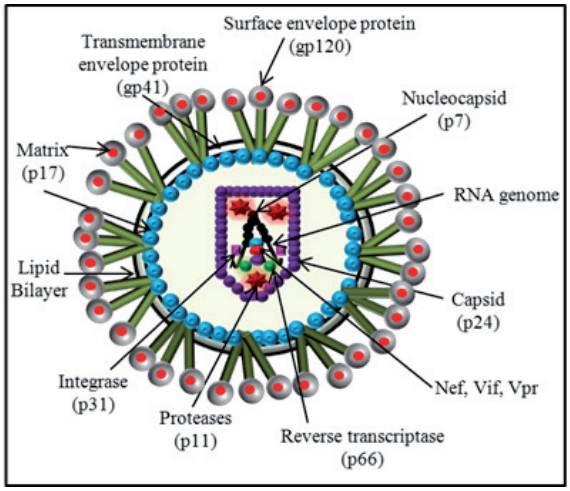

Figure 1: Schematic illustration of HIV virion showing its pivotal proteins and RNA genome, encapsulated in nucleocapsid. Adapted from [18] and redrawn

conformational changes culminating in virus and host cell membrane fusion. Most primary HIV-1 strains use the chemokine receptor CCR5 as coreceptor in conjunction with CD4 for virus entry. However, some strains have evolved to use related receptors [24]. Binding of gp120 to CD4 causes conformational changes observable in variable loop regions V1/V2 and V3, causing the V3 loop to evaginate, and thus becoming exposed to the coreceptors [25]. The precise mechanisms of interaction between V1/V2, V3 and chemokine receptors are not well understood [26]. The final step of viral entry, fusion of the viral components with target membrane, is achieved by gp41 [27,28]. After binding of gp120 to CD4 and coreceptors, conformational changes occur, leading to gp41 unfolding and the hydrophobic fusion peptide sequence extends towards the host cell membrane [29]. The insertion of the peptide leads to fold into a hairpin-like structure, believed to be responsible for the fusion of the HIV to the host cell [30].

4. Potential vaccines based on interaction antibody-CD4 binding site

Due to the nature of fusion, there are several possible targets for the development of drugs with synergistic effects on inhibition of viral entry steps, at which the interference can be attempted [18]. Generally, these targets may affect viral entry by the inhibition of CD4 binding due to a blocking of conservative CD4 binding site of gp120. Hence, glycoprotein cannot interact with receptors and coreceptors and process of conformational changes, whereas the triggering the fusion is stopped.

The first HIV CD4 binding site of gp120-specific human monoclonal antibody (mAb), b12, was identified in 1994 by Burton and colleagues [31]. It can bind to gp120 via CD4bs and successfully compete with soluble CD4 for binding to gp120. Nevertheless, the breadth of neutralization is limited either by variations in sequence of CD binding site or by distal mutations, affecting accessibility of b12 to its epitope [32]. Thus, it was shown that proper positioning of the gp120 plays crucial role for antibody for effective CD4 binding site recognition.

Currently, RV144, also known as the Thai trial (clinical trial, phase III) is the only HIV-1 vaccine demonstrating efficacy against HIV-1 acquisition. RV144 combines two vaccines (ALVAC/AIDSVAX) that failed, during vaccinating in Thailand in 2003 until 2006 [33]. The major components of RV144 are the antibodies (CH58 and CH59) against the V1V2 region of gp120 and it was revealed that these antibodies seem to play a predominant role in protection against HIV-1 acquisition [34]. CH58 and CH59 could bind to gp120 antigen and also to a HIV-1 envelope variable region 2 peptide [35], and thus work as the broadly neutralizing antibodies for HIV-1 management.

5. Conclusion

Exterior envelope glycoprotein gp120 is a unique protein structure, fundamental for HIV attachment to specific cell surface receptors and HIV entry into cells. Inhibition of such interaction is a „holy grail“ in development of vaccines for HIV management; however targeting gp120 has proven extremely difficult, particularly due to its shielding and partial variability. Further research of novel antibodies towards the most conservative sites of CD4 binding site of gp120 can thus led us to success as is currently shown in phase III by a mixture of monoclonal antibodies - RV144.

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Conflicts of Interest

The authors declare they have no potential conflicts of interests concerning drugs, products, services or another research outputs in this study. The Editorial Board declares that the manuscript met the ICMJE „uniform requirements“ for biomedical papers.

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