

HIV-1 Envelope Glycoprotein Structure and Immunogenicity

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The HIV-1 exterior envelope glycoprotein, gp120, and the transmembrane glycoprotein, gp41, are non-covalently associated trimers of heterodimers that form the surface unit functional spike. The gp120 molecule engages the primary receptor, CD4, and co-receptor, CCR5 and, following conformational changes, gp41 mediates viral-to-cell membrane fusion and entry. As the sole virally encoded products on the viral surface, the envelope glycoproteins are the major targets for neutralizing antibodies. Infection of human individuals elicits neutralizing antibodies, which, along with host cellular responses, select for persistently replicating viral variants that are usually highly resistant to host immunity, especially neutralizing antibodies. Due to error prone reverse transcriptase and the ability of functional envelope glycoproteins to tolerate considerable variability, a wide array of HIV primary isolates bearing heterogeneous spikes evolve in both the individual and the human population. To date, only four broadly neutralizing antibodies have been isolated from infected individuals and none have been elicited by multiple vaccine strategies, including subunit HIV-1 envelope glycoprotein design. Efforts are underway to map the neutralizing activity in HIV patients displaying broad neutralization and to obtain more broadly neutralizing antibodies. Structural, antigenic, biochemical and biophysical analysis of the HIV-1 envelope glycoproteins are ongoing to better understand the immune evasion properties that evolve in the HIV envelope glycoproteins and selected data will be described. We are pursuing the hypothesis that such information will impact favorably upon rational immunogen design to better elicit broadly neutralizing antibodies as a component of an effective HIV-1 vaccine.