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RETROVIROLOGY

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Molecular architecture of the uncleaved HIV-1 envelope glycoprotein trimer

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The human immunodeficiency virus (HIV-1) envelope glycoprotein (Env) trimer, a membrane-fusing machine, mediates virus entry into host cells and is the sole virus-specific target for neutralizing antibodies. Binding the receptors, CD4 and CCR5/CXCR4, triggers Env conformational changes from the metastable unliganded state to the fusion-active state. We used cryo-electron microscopy to obtain a 6-Å structure of the membrane-bound, heavily glycosylated HIV-1 Env trimer in its uncleaved and unliganded state. The spatial organization of secondary structure elements reveals that the unliganded conformations of both gp120 and gp41 subunits differ from those induced by receptor binding. The gp120 trimer association domains, which contribute to interprotomer contacts in the unliganded Env trimer, undergo rearrangement upon CD4 binding. In the unliganded Env, intersubunit interactions maintain the gp41 ectodomain helical bundles in a "spring-loaded" conformation distinct from the extended helical coils of the fusion-active state. Quaternary structure regulates the virus-neutralizing potency of antibodies targeting the conserved CD4-binding site on gp120. Recent studies that help validate the 3-D reconstruction of the unliganded HIV-1 Env precursor map will be presented. The Env trimer architecture provides mechanistic insights into the metastability of the unliganded state, receptor-induced conformational changes, and quaternary structure-based strategies for immune evasion.

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