High Resolution Studies of the Full Length HIV-1 Env Trimer

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Ever since the introduction of human immunodeficiency virus (HIV) into the human population around 50 years ago, it has become a persistent pandemic infecting millions of people worldwide. As of now there is no cure for HIV/AIDS, and the available treatments that help alleviate symptoms and prolong life are not readily accessible to the majority of HIV patients living in third world countries. In order to curb the epidemic, researchers have conducted over 30 clinical trials with vaccine candidates since 1987, albeit without success. Vaccines work by training the immune system against viral proteins prior to infection, such that it readily produces antibodies that recognize the foreign viral component upon infection. In HIV, this antigen is called the envelope glycoprotein (Env), which forms a trimeric spike embedded on the viral membrane on the surface of the virus, where each of the three pillars within the trimer consists of two protein components, gp120 and gp41. The failure in vaccine development has been due to the numerous tactics employed by HIV to escape the surveillance by immune system. These include gp120 shedding which reduces the number of spikes available for recognition by the immune system, a shield of carbohydrates around gp120 that makes it look less foreign, and high mutation rates resulting in a lack of a consistent target for antibodies produced.

The recent fortuitous discovery of broadly neutralizing antibodies (bNAbs) that are able to potently disable diverse HIV strains lead to the idea of engineering an Env based vaccine that is able to elicit the same bNAb responses. In order to illustrate how bNAbs interact with Env, I will utilize electron microscopy (EM) to take high magnification pictures of Env-antibody complexes. From these 2D images I will use computational methods to create 3D models showing how these proteins interact. Because many of the previous structural studies of Env proteins have only visualized small fragments, I will focus my studies on the full length protein in its native membrane environment. The models generated from these studies will provide hints as to which regions of Env are the most vulnerable and why, what specific shape Env has to assume for recognition by antibodies to be possible, and how these antibodies neutralize HIV activity by binding to Env. The knowledge garnered from structural studies can aid in the design of an Env protein that behaves and is recognized by the immune system in a manner able to drive antibody response upon future infection.