Molecular Characterization of the HIV-1 N332 Epitope-Cluster

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2014

By inflicting the acquired immune deficiency syndrome (AIDS) the human immunodeficiency virus (HIV) has claimed about 25 million lives over the past three decades. Even though AIDS has become more manageable through the development of highly effective drugs, viewer than 25% of the estimated 34 million people living with HIV today are actually being treated for various reasons - as a consequence, about 2.5 million people are newly infected with the virus every year.

To counter-act the untamed spread of the virus, researchers have been seeking to create an HIV vaccine ever since the relation between HIV and AIDS has been established. The general idea of vaccination is to alert the human body's own defenses, the immune system, by challenging it with a safe substance, a vaccine or immunogen that mimics the real virus in its molecular characteristics. In response, the immune system elicits specifically tailored proteins called antibodies that ideally bind and neutralize the vaccine as well as the actual virus upon infection, thereby providing immunity. In the case of HIV, the only target accessible to the immune system is the envelope protein (Env), which is comprised of two subunits gp120 and gp41. These subunits form a trimer of dimers on the viral surface, the Env spike, which the virus uses to dock onto and infect immune cells. Hence, most vaccination efforts aim at inducing anti-HIV neutralizing antibodies focused on various forms of trimeric Env, gp120 or gp41 to induce protective immunity against HIV. Unfortunately, no vaccine trial in the past 25 years has been successful at protecting individuals against the vast array of circulating viral strains. The reasons for that, while diverse and in part not well understood, are foremost the very high mutation rate of the virus, which continuously alters the target presented to the immune system, and the dense attachment of sugars - so called glycans - to gp120 and gp41, which disguises these proteins and makes them appear less dangerous, thus misleading the immune system.

Hopes for a universal vaccine were recently reinvigorated with discovery of broadly neutralizing antibodies (bNAbs) in a subset of long term infected HIV patients. These antibodies have the ability to neutralize a vast majority of commonly observed HIV strains, thereby taking away the mutational edge the virus has in its arms race against the immune system. BNAbs are known to bind four distinct areas, so called epitopes, on gp120 and gp41. The most potent known bNAbs attack the epitope cluster surrounding the glycan attached to asparagine 332 (N332) on gp120. Only few such bNAbs are known and thoroughly characterized to date.

To enable the design of immunogens mimicking the most broadly and potently neutralized areas of the N332 epitope cluster, my research aims at isolating novel bNAbs from a small panel of long term infected donors with variously broad and potent blood serum responses against the epitopes in question and to biochemically, structurally and genetically characterize these bNAb families and their binding sites. Ideally, the insights gained from this study can make specific and detailed suggestions as to what parts of the N332 epitope cluster vaccine candidates need to resemble in order to present an easy-to-recognize target to the immune system that can induce a focused, potent and broadly neutralizing immune response - potentially protecting from HIV infection.