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DISSERTATION

"Mapping of novel amino acids and larger determinants in the HIV-1 Env affecting conformational masking and resistance to neutralizing mAbs"

by

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1:00 PM
International Center for Public Health, PHRI Board Room (E250M)

Abstract

Despite the major advances in antiretroviral treatment, immunotherapy, and vaccine development of the past 30 years, a definitive long-term cure for infected individuals and an effective vaccine preventing HIV-1 infection in exposed individuals remains elusive. One challenge hampering vaccine efficacy and the prevention of viral rebound after treatment interruption is the high mutation rate of the virus. This leads to the rapid loss of epitopes and a less documented more indirect fluctuation in the conformational state of Env, the sole immune target on the viral surface, which in turn alters viral susceptibility to neutralization by neutralizing antibodies. Another challenge hampering vaccine success is the inability to identify an appropriate antigen necessary to stimulate a protective immune response against a wide breadth of viruses instead of a response excessively focused on immunodominant, non-protective Env epitopes. Analysis of prior vaccine efforts indicate that a better understanding of the natural conformational diversity and plasticity leading to the masking or exposure of epitopes in Env will be crucial to overcoming these challenges. For example, conformational masking by the gp120 V1/V2 domain of Env, mediated by glycans and other amino acid changes in this region, is a well-studied regulator of neutralization phenotype. However, for many viruses, neutralization phenotype is not predicted by V1/V2 sequence alone. Therefore, in this dissertation, we sought to identify additional mechanisms accounting for the resistance of natural HIV-1 isolates to neutralization by commonly-induced antibody responses. We identified three separate mechanisms that influence neutralization sensitivity independently of the standard V1/V2 masking effect. For CM244/TH023 this includes the addition of glycosylation sites outside of the V1/V2 domain that mask key epitopes. For WITO/SF162 this involves differences in the Env leader sequence, C1, and gp41 domain, which alters the neutralization phenotype of an Env without a highly masking V1/V2, while for MW965/ConC this involves two novel mutations in the conserved C3 and C5 regions that influence conformational flexibility of the V1/V2. Additionally, the differing effects on viral infectivity and/or Env processing, observed with each set of mutations, demonstrates that some residues have negative impacts on viral fitness and may explain the rarity of these identified substitutions. Taken together, the results presented here highlight the intrinsic plasticity of Env and point to the importance Env conformational state may play in the induction of a desired immune response in future vaccination and therapeutic settings.