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Elicitation of broadly reactive antibodies against glycan-modulated neutralizing V3 epitopes of HIV-1 by immune complex vaccines

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Abstract

HIV-1 envelope gp120 is the target for neutralizing antibodies (NAb) against the virus. Various approaches have been explored to improve immunogenicity of broadly neutralizing epitopes on this antigen with limited success. We previously demonstrated that immunogenicity of gp120 and especially its V3 epitopes was enhanced when gp120 was co-administered as immune-complex vaccines with monoclonal antibodies (mAb) to the CD4-binding site (CD4bs). To define the mechanisms by which immune complexes influence V3 immunogenicity, we compared gp120 complexed with mAbs specific for the C2 region (1006), the V2 loop (2158), or the CD4bs (654), and found that the gp120/654 complex was the most potent in eliciting anti-V3 NAbs. The other complexes stimulated no or lower levels of anti-V3 Nabs. gp120 complexed with 654 $F(ab')_2$ was as potent, indicating that V3 immunogenicity is determined by the specificity of the mAb Fab fragment used to form the complexes. Importantly, the gp120/654 complex not only induced anti-gp120 Abs to higher titers, but also of greater avidity. The Abs was cross-reactive with V3 peptides from most subtype B and some subtype C isolates. Neutralization was detected only against Tier-1 HIV-1 pseudoviruses, while Tier-2 viruses, including the homologous JRFL strain, were not neutralized. However, JRFL produced in the presence of a mannosidase inhibitor was sensitive to anti-V3 Nabs in the immune sera. These results demonstrate that the gp120/654 complex is a potent immunogen for eliciting cross-reactive functional NAbs against V3 epitopes, of which exposure is determined by the specific compositions of glycans shrouding the HIV-1 envelope glycoproteins.

Biography

Dr. Catarina Hioe is a Research Career Scientist at the VA New York Harbor Healthcare System, Manhattan Campus and an Associate Professor in the Department of Pathology, New York University School of Medicine. Dr. Hioe's lab has been studying immune responses to HIV envelope gp120 and gp120-mediated immunopathogenesis for more than 10 years. She has pioneered the development of immune complexes as vaccines to target neutralizing epitopes on HIV envelope gp120. She has published over 40 research and review papers. She currently serves as an editor for Frontiers in Immunotherapies and Vaccines and adhoc reviewer for multiple journals including PLoS One and Vaccine. She is also a member of the NIH study section on HIV/AIDS Vaccine.