Structural Basis of HIV-1 Neutralization: Implications for Vaccine Design

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Antibodies that can potently neutralize a broad spectrum of HIV-1 primary isolates are extremely rare and invaluable for innovative HIV-1 vaccine design strategies. Crystal structures for four of the five antibodies [b12; 2G12; 447-52D; and 4E10] have been determined. Antibody b12 interacts with the recessed CD4 binding site through a long CDR H3 loop. Anti-gp120 antibody 2g12 recognizes a cluster of high-mannose sugars on the surface of gp120—an unexpected high affinity for a carbohydrate epitope. The 2g12 Fab arms dimerize via exchange of their V_H domains to form a multivalent binding surface for carbohydrates that is useful for designing a carbohydrate-based vaccine. Antibody 447-52D also uses a long CDR H3 loop, but it interact with the V3 loop backbone of gp120, which explains its broad specificity. 4E10 is the most broadly neutralizing and is effective against all clades and subtypes of HIV-1. The 4E10 structure with a gp41 peptide shows a helical conformation for the epitope that gives insights into the membrane fusion events. Thus, these structural studies not only elucidate how each antibody interacts with its respective antigenic site in either gp120 or gp41, but also give fascinating insights into how the immune system evolves strategies to overcome challenges in accessing epitopes that are deeply-buried (b12), have low antigenicity (2g12), that vary in sequence (447-52D), and are transiently-accessible (4E10). The novel modes of antigen recognition provide a plethora of new ideas for the design of novel HIV-1 immunogens to elicit such antibody responses and are being harnessed in a retrovaccinology approach for HIV-1 vaccine design.

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