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Prospective clinical utility and evolutionary implication of broadly neutralizing antibody fragments to HIV gp120 superantigenic epitope

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Background: Neutralizing antibodies (Abs) that neutralize diverse strains found across the world are needed to develop effective HIV immunotherapies and topical immunomicrobicides. Residues 421-433 constitute a conserved epitope overlapping the CD4 receptor binding and B cell superantigenic sites of gp120. Abs to this epitope from uninfected humans bind and catalyze the hydrolysis of gp120, resulting in modest HIV neutralization. We describe here the anti-HIV properties of Ab fragments from patients with lupus, a disease rarely coexistent with HIV infection.

Methods: Single chain Fv (scFv) clones were selected from phage displayed lupus repertoires using gp120 and its electrophilic analogs (E-gp120). Neutralization of clinical HIV isolates by purified Ab fragments was measured by p24 assays using peripheral blood mononuclear cells. gp120, E-gp120 and E-416-433 binding and hydrolysis were determined by ELISA and electrophoresis. Framework (FR) replacement was by PCR mutagenesis.

Results: Selected scFv clones displayed gp120 binding and hydrolyzing activities attributable to 421-433 peptide recognition. Sub- μ g to μ g/ml scFvs neutralized all CCR5-dependent clade A, B, C, D and AE viruses tested (18-20 strains). scFv potencies and neutralization breadths were superior to IgG b12. Pseudovirions derived from neutralizable clinical isolates were not neutralized. CXCR4 strains were neutralized poorly. Replacements of Replacing VH FR1 and FR3 in a VH4-family scFv with the FRs from a VH3-family scFv improved the binding of E-gp120 and E-peptide, consistent with the belief that superantigens are recognized at FRs, and contrasting with adaptive recognition of conventional antigens at the hypervariable CDRs.

Conclusion: The unprecedented potency and breadth of HIV neutralization revive hopes of producing effective immunotherapeutic and microbicidal Abs at affordable cost. Recognition at the FRs of Abs suggests that an ancient antigenic homolog of the gp120 superantigenic region guided the evolution of germline genes encoding the HIV neutralizing Abs. Supported by NIH.