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Survivors of HIV infection produce potent, broadly neutralizing IgAs directed to the superantigenic region of the gp120 CD4 binding site

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Background: HIV disease progression can occur slowly. Preimmune antibodies (Abs) recognize the conserved 416-433 residues in the B cell superantigenic determinant of gp120, which also contains essential amino acids necessary for HIV binding to CD4 receptors. We previously identified IgAs in uninfected humans that recognize the 416-433 epitope, catalyze the degradation of gp120 and neutralize HIV with modest potency. Here, we report the anti-HIV properties of IgAs from long-term survivors of HIV infection.

Methods: Neutralization of clinical HIV isolates by purified plasma IgA was measured by p24 assay using peripheral blood mononuclear cells. Binding of electrophilic analogs of gp120 V3 peptide 306-328 (E-306-328) and CD4 binding peptide 416-433 (E-416-433) was determined by ELISA. gp120 hydrolysis was monitored electrophoretically.

Results: Sub- μ g to μ g/ml purified IgAs from 3 hemophilia A subjects with 17-21 years clade B infection and little or no anti-retroviral therapy (S_{17-21} survivors) neutralized all 18 heterologous, CCR5-dependent strains tested (clade A, B, C, D and AE). Neutralization potencies and breadths were favorable compared to monoclonal IgG b12; IgAs from uninfected subjects; and IgAs from infected subjects who succumbed to AIDS or survived without AIDS for 5 years. CXCR4-dependent strains were neutralized poorly. Pseudovirions of certain neutralizable clinical isolates were not neutralized. S_{17-21} IgAs hydrolyzed recombinant gp120 detectably and displayed binding of E-gp120, V3 E-306-328 and the superantigenic E-416-433 peptide. Depletion of the E-416-433 binding IgA subset resulted in loss of HIV neutralizing activity.

Conclusion: Potent and broad HIV neutralization suggest that the IgAs slow the progression of HIV disease. The superantigenic character of the 416-433 epitope may explain the unusual adaptive IgA response occurring very late in infection. The IgA properties identify the 416-433 epitope as a suitable target for vaccine-induced prophylaxis against the virus. Supported by NIH grants AI058865, AI067020, AI071951, AI062455.