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Poster presentation

P04-44. Generation of antibody responses to HIV-1 membrane proximal external region (MPER) antigen

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Background

Immune responses to HIV-1 rarely generate broadly cross-reactive, neutralizing antibodies (NAb). Some NAbs are polyreactive and bind self-antigens, suggesting that effective humoral responses to some HIV-1 antigens are constrained by tolerization of NAb B cells.

Methods

The human HIV-1 NAb 2F5 was used to identify human and mouse self-antigens that cross-react with the gp41 MPER. Mouse B cells were generated absent the tolerizing environment of bone marrow (BM) in sequential cultures of non-adherent progenitor cells containing rIL-7, and later, rBAFF. RAG1-deficient mice were reconstituted with culture derived (CD) B and T cells (CD-RAG mice); 4 wks later serum immunoglobulin and autoantibody were quantified. CD-RAG and control mice were immunized with HIV-1 gp-41 MPER antigen in alum adjuvant; germinal center (GC) and antibody responses were determined 2 weeks after primary or boost immunizations.

Results

The 2F5 NAb binds to nuclear antigens in both uninfected human and mouse cells. BM and CD transitional B cells are enriched for reactivity to self and to an MPER antigen. Sera of CD-RAG and control mice have similar IgM/IgG serum levels but autoantibody titers are greatly elevated in CD-RAG animals. MPER antigen was weakly immunogenic in C57BL/6 mice, but MPER immunization of CD-RAG mice elicited strong (4-fold higher) GC responses and ~30-fold more MPER IgG antibody.

Conclusion

The 2F5 NAb binds to phylogenetically conserved nuclear antigens, consistent with the hypothesis that HIV-1 evades humoral immunity by exploiting immunological tolerance. We show that transitional B cells generated *in vitro* are enriched for autoreactive cells which survive and reconstitute serum antibody *in vivo*. Immunization of autoimmune CD-RAG mice with an MPER antigen results in significantly higher GC and antibody responses compared to intact controls. The CD-RAG mouse is a novel model for investigating ''forbidden'' humoral responses to HIV-1 antigens.