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Poster presentation

P04-26. Immunological tolerance prevents the expression of a broadly reactive neutralizing HIV-1 antibody

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Background

Developing a safe and effective HIV-1 vaccine has been hampered by the inability to design immunogens that can induce antibodies capable of potently neutralizing diverse HIV-1 strains. Despite the recognition of conserved HIV-1 envelope (Env) regions by rare, broadly neutralizing antibodies, these regions fail to induce protective antibodies when used as immunogens or in the context of natural infections. Various hypotheses have been offered to explain the absence of an effective immune response to Env determinants, including the suppression of this response by immunological tolerance. This hypothesis arose from the observation that broadly neutralizing HIV-1 antibodies can cross-react with self-antigens.

Methods

To test the tolerance hypothesis, we generated a knock-in mouse strain, 2F5 V_H, in which the immunoglobulin (Ig) heavy chain variable region rearrangement ($V_HD_HJ_H$) of the broadly neutralizing human antibody 2F5 was targeted into the J_H cluster of the mouse Igh locus.

Results

In vitro, chimeric human/mouse 2F5 antibodies were functionally equivalent to the human 2F5 antibody. *In vivo*, the 2F5 V_H insertion resulted in a profound B cell developmental blockade in the bone marrow with >80% loss of immature B cells. Furthermore, both 2F5 $V_{H^{+/-}}$ and 2F5 $V_{H^{+/+}}$ mice lacked serum reactivity to cardiolipin and nuclear antigens, yet had detectable, albeit severely diminished, mature splenic B cell populations. In 2F5 $V_{H^{+/-}}$ mice, the majority of remaining mature splenic B cells used endogenous heavy chains, indicating loss of effective allelic exclusion.

Conclusion

The 2F5 V_H knock-in phenotype identifies a profound effect of tolerance mechanisms on suppressing 2F5 antibody heavy chain-expressing B cells, and is similar to that seen in other knock-in strains expressing Ig heavy chains of autoreactive antibodies. This mouse strain will be useful for developing immunization strategies to circumvent tolerance mechanisms and safely induce broadly neutralizing antibodies against the gp41 membrane proximal external region.