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HIV

A recipe for inducing broadly neutralizing antibodies

> the immune profile associated with bnAb production is a result of perturbations induced by virus infection

The design of immunogens that induce broadly neutralizing antibodies (bnAbs) is the holy grail of HIV-1 vaccine research, and much effort has been devoted to studying the structural mode of target recognition by these antibodies (see Further reading). However, only rarely do HIV-1-infected individuals make high levels of bnAbs. What can we learn from the immune profiles of HIV-1-infected individuals about the mechanisms that determine whether or not bnAbs are produced?

The authors examined a cohort (Cohort A) of 239 HIV-1-infected individuals (90% African), from which 51 individuals with the highest levels of bnAbs were selected (the A.bnAb group) and matched with 51 individuals who did not produce bnAbs (the A.control group). 65% of the A.bnAb group had plasma autoantibodies, compared with 31% of the A.control group. A similar correlation between autoantibody production and induction of bnAbs was noted in a second cohort of HIV-1-infected individuals from the United States. By contrast, there was no difference in the plasma antibody response to an influenza virus antigen between bnAb and control groups in either cohort, which indicates that the increased frequency of autoantibodies in the bnAb group is not the result of a general increase in antibody production and may result from alterations to immune tolerance.

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The frequency of memory T follicular helper (T_{FH}) cells (defined as $PD1^+CXCR3^-CXCR5^+CD4^+$ cells) was significantly higher in the A.bnAb group than the A.control group, whereas the frequency of $CD4^+CD25^+FOXP3^+$ regulatory T (T_{reg}) cells within lymphocytes was lower in the A.bnAb group. Furthermore, T_{reg} cells in the A.bnAb group — including a regulatory population of T_{FH} cells (known as T_{FR} cells) — expressed significantly higher levels of the inhibitory receptor PD1 compared with the A.control group.

Higher levels of PD1 expression on T_{reg} and T_{FR} cells are indicative of increased activation and, potentially, dysfunction. Levels of the activation marker HLA-DR and the exhaustion markers CTLA4 and LAG3 were higher on T_{reg} cells from the A.bnAb group than the A.control group, and expression of these markers correlated with PD1 expression. Importantly the $PD1^{hi}$ T_{reg} cells from A.bnAb individuals had impaired ability to suppress the proliferation of conventional $CD4^+$ T cells.

Together, the results indicate that an immune profile of increased autoantibody production, increased T_{FH} cells, decreased T_{reg} cells and increased PD1 expression by T_{reg} and T_{FR} cells is associated with the production of bnAbs. However, analysis of HIV-1-seronegative individuals with or without autoantibodies indicated that there are no significant differences in terms of this immune profile before HIV-1 infection that could account for the differential antibody response. There were also no significant differences in terms of HLA class I and II allotypes between the A.bnAb and A.control groups, and whole exome sequencing found no statistically significant mutations that are associated with bnAb production.

Hence, the authors conclude that the immune profile associated with bnAb production is a result of perturbations induced by virus infection, although they do not rule out the contribution of pre-existing abnormalities in host tolerance in certain individuals. Determining the mechanism of these virus-induced perturbations will be key to designing an effective vaccine strategy.

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ORIGINAL ARTICLE Moody, M. A. *et al.* Immune perturbations in HIV-1-infected individuals who make broadly neutralizing antibodies. *Sci. Immunol.* **1**, aag0851 (2016)
FURTHER READING Kwong, P. D. *et al.* Broadly neutralizing antibodies and the search for an HIV-1 vaccine: the end of the beginning. *Nat. Rev. Immunol.* **13**, 693–701 (2013)