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ANTIBODIES

Want to neutralize HIV? Get help!

Recent studies suggest that the control of HIV progression in rare individuals involves the generation of broadly neutralizing antibodies, which undergo extensive affinity maturation in the germinal centres. Reporting in *Immunity*, Locci *et al.* identify a population of circulating T follicular helper (T_{FH}) cells that support this process and that correlate with the generation of broadly neutralizing antibodies in individuals with HIV infection.

On the basis of the premise that HIV-infected individuals who make broadly neutralizing antibodies might have 'better' T_{FH} cell responses than those who do not, the authors screened a large cohort of HIV-infected individuals at several time points. Initial analysis showed no correlation between total $CD4^+$ T cells that express the T_{FH} cell marker CXC-chemokine receptor 5 (CXCR5) and the presence of broadly neutralizing antibodies. However, a subset of these circulating $CXCR5^+CD4^+$ cells expressing programmed cell death protein 1 (PD1) at low to moderate levels were identified that most closely resembled germinal centre T_{FH} cells from the tonsils and that had a quiescent, memory-like phenotype. Indeed, this $PD1^+CXCR3^-CXCR5^+CD4^+$ population produced high levels of the factors that are required for T_{FH} cells to help B cells — that is, interleukin-21 (IL-21), IL-4 and CXC-chemokine ligand 13 (CXCL13). Studies *in vitro* confirmed their superior ability compared with other T cell populations to induce memory B cell differentiation to IgG-secreting plasma cells.

> "the frequency of the functional memory T_{FH} cells … correlated with the capacity … to subsequently develop broadly neutralizing antibodies"

Re-evaluation of the association between $CXCR5^+CD4^+$ cell subsets and the development of broadly neutralizing antibodies against HIV indicated that, at the earliest available time point, the frequency of the functional memory T_{FH} cells ($PD1^+CXCR3^-CXCR5^+CD4^+$) correlated with the capacity of individuals to subsequently develop broadly neutralizing antibodies. This correlation also remained strong at later time points.

So, the ability of rare HIV-infected individuals to develop broadly neutralizing antibodies against HIV depends on the presence of $PD1^+CXCR3^-CXCR5^+CD4^+$ T_{FH} cells in the blood. This suggests that a candidate HIV vaccine that is designed to boost this subset of T cells would be a promising prophylactic or therapeutic approach.

Lucy Bird

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ORIGINAL RESEARCH PAPER Locci, M. *et al.* Human circulating $PD\text{-}1^+CXCR3^-CXCR5^+$ memory Tfh cells are highly functional and correlate with broadly neutralizing HIV antibody responses. *Immunity* http://dx.doi.org/10.1016/j.immuni.2013.08.031 (2013).