ANTIVIRAL IMMUNITY

Deconstructing CD4$^+$ T cell memory

By analysing the function of memory CD4$^+$ T cells specific for influenza A virus in unprimed hosts — in the absence of virus-specific memory B cells, antibodies or memory CD8$^+$ T cells — this study deconstructs the protective mechanisms of CD4$^+$ T cell memory. It shows that memory CD4$^+$ T cells use multiple mechanisms both alone and in synergy with other lymphocytes to mediate optimal antiviral immunity. This suggests that the induction of memory CD4$^+$ T cells by influenza A vaccines should be given greater consideration.

Transfer of T cell receptor-transgenic (HNT) memory CD4$^+$ T cells that recognize the PR8 strain of influenza A virus to wild-type mice protected against challenge with the PR8 virus in a dose-dependent manner. Memory CD4$^+$ HNT cells protected against a high dose of PR8 (10,000 EID_{50} (50% egg infective dose)) in wild-type mice, whereas naive HNT cells provided no protection. B cell-deficient (J_HD) and T cell-deficient (nude) mice succumb to a lower dose of PR8 (2,500 EID_{50}) than do wild-type mice, but they were completely protected by the transfer of memory CD4$^+$ HNT cells. However, transfer of memory CD4$^+$ HNT cells could not protect J_HD or nude mice against a high dose of PR8, which shows that optimal protection against high virus titres requires synergy between memory CD4$^+$ T cells and both naive B cells and naive T cells. In the absence of both B and T cells, severe combined immunodeficiency (SCID) mice that received memory CD4$^+$ HNT cells all succumbed to the lower dose of PR8, although the memory cells did increase the mean survival time of SCID mice. Furthermore, memory CD4$^+$ T cells could protect SCID mice against a very low dose (500 EID_{50}) of PR8.

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Together, the results show that, as the virus dose increases, memory CD4$^+$ T cells need to expand their protective mechanisms to include cooperation with B and T cells. In line with this, the co-transfer of naive B cells or naive CD8$^+$ T cells with memory CD4$^+$ T cells restored complete protection against 2,500 EID_{50} of PR8 in SCID mice. The memory CD4$^+$ T cells directly synergize with virus-specific neutralizing antibodies, and this synergy does not involve T cell help for germinal centre responses. Similarly, there was no effect of CD4$^+$ T cells on the magnitude or kinetics of the CD8$^+$ T cell response. So, the helper function of memory CD4$^+$ T cells is not required for their antiviral synergy with B cells or CD8$^+$ T cells, which suggests that it is the effector mechanisms of these cell types that synergize rather than the cells themselves.

One such antiviral mechanism of memory CD4$^+$ T cells is perforin-dependent cytotoxicity. SCID hosts that received perforin-deficient memory CD4$^+$ HNT cells had higher viral titres after PR8 infection than mice that received wild-type HNT cells. The antiviral effects of memory CD4$^+$ T cells alone were shown to be completely dependent on interferon-γ production, but this cytokine was not required for synergy with B cells or CD8$^+$ T cells.

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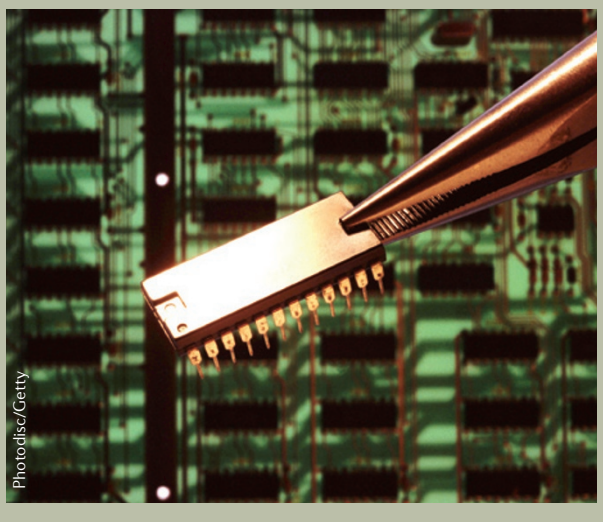

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ORIGINAL RESEARCH PAPER McKinstry, K. K. *et al.* Memory CD4$^+$ T cells protect against influenza through multiple synergizing mechanisms. *J. Clin. Invest.* **122**, 2847–2856 (2012)
FURTHER READING Swain, S. L. *et al.* Expanding roles for CD4$^+$ T cells in immunity to viruses. *Nature Rev. Immunol.* **12**, 136–148 (2012)