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NATURAL KILLER CELLS

Making memories

The ability to generate antigen-specific memory responses is classically regarded as a hallmark of the adaptive immune system. However, recent evidence suggests that natural killer (NK) cells of the innate immune system can also be long-lived and generate enhanced responses on secondary encounter with antigen. Paust *et al*., reporting in *Nature Immunology*, extend these observations and show that a subset of NK cells in the liver acquires antigen-specific memory to various haptens and viruses, and that this capacity depends on their expression of CXC-chemokine receptor 6 (CXCR6).

Consistent with previous studies, the authors first showed that NK cells that were sensitized to a hapten and then transferred into lymphopenic recipient mice that lack T cells, B cells and NK cells (*Rag2*$^{-/-}$*Il2rg*$^{-/-}$ mice) retained memory for the hapten when it was applied to one ear of the recipient mice 4 months later. Interestingly, only NK cells isolated from the liver, and not from the spleen, of sensitized donor mice mediated the hapten-induced contact hypersensitivity (CHS) response in recipient mice, suggesting that this is a unique property of hepatic NK cells. Moreover, the recall response was hapten specific because hepatic NK cells that were sensitized with a different hapten to that used for the secondary challenge failed to mediate inflammatory recall responses in challenged recipient mice and did not accumulate at the challenge site.

Next the authors showed that NK cell memory can develop following sensitization with non-infectious virus-like particles that contain influenza virus antigens (PR8-VLPs) or HIV-1 antigens, or with ultraviolet-inactivated vesicular stomatitis virus. Again, this feature was unique to hepatic NK cells and occurred in a virus-specific manner. Importantly, antiviral NK cell memory conferred protection against lethal viral challenge: *Rag2*$^{-/-}$*Il2rg*$^{-/-}$ mice given PR8-VLP-primed hepatic NK cells and challenged 3 months later with a lethal dose of influenza virus survived longer than naive mice or mice given PR8-VLP-primed splenic NK cells.

Contrary to previous studies — which showed that NK cell memory for murine cytomegalovirus depends on recognition of the virus by the NK cell receptor LY49H (also known as KLRA8) — NK cells did not seem to use any of their known pattern recognition receptors to recognize influenza virus antigen for sensitization and protection against influenza virus infection. Instead, the NK cell memory response required expression of CXCR6. Accordingly, 35–55% of hepatic NK cells, but only 3–5% of splenic NK cells, expressed CXCR6. By tracking CXCR6 expression with a fluorescent marker, it was shown that only the CXCR6-expressing sensitized NK cells elicited CHS responses following transfer into lymphopenic recipients. In addition, *Cxcr6*$^{-/-}$ mice had impaired NK cell memory responses compared with their *Cxcr6*$^{+/-}$ littermates.

However, the role of CXCR6 seems complex. As expected, treatment with a CXCR6-specific blocking antibody decreased NK cell-mediated CHS responses to haptens and protection against viral infection. However, unexpectedly, addition of this antibody to *in vitro* cytotoxicity assays led to increased killing of haptenated B cells by *Cxcr6*$^{+/-}$ NK cells, whereas addition of the CXCR6 ligand, CXCL16, attenuated NK cell cytotoxicity. So the authors suggest that continuous CXCR6 signalling in hepatic NK cells, provided by constitutive expression of CXCL16 in the liver sinusoids, promotes long-term persistence and effector potential of memory NK cells, while protecting against NK cell-mediated hepatotoxicity by preventing full killing activity.

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ORIGINAL RESEARCH PAPER Paust, S. *et al.* Critical role for the chemokine receptor CXCR6 in NK cell-mediated antigen-specific memory of haptens and viruses. *Nature Immunol.* 24 Oct 2010 (doi:10.1038/ni1953)

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