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INNATE IMMUNITY

Memory NK cells identified in primates

The first demonstration that primates possess antigen-specific natural killer (NK) cells mediating long-term memory is provided by a new study in rhesus macaques. NK cells are a key component of the innate immune system and can cooperate with antibody- and T cell-mediated adaptive immunity, but accumulating evidence indicates that they also have independent antigen specificity. Antigen-specific NK cell memory has been reported in mice lacking B cells and T cells, in which memory NK cells develop in the liver after exposure to haptens and viral antigens. However, the presence of these cells in primates had not been conclusively shown.

Reeves *et al.* used magnetic beads and flow cytometry to purify NK cells from the spleen or liver of rhesus macaques infected with simian–human immunodeficiency virus $(SHIV)_{SF162P3}$ and to confirm a lack of T cell contamination. Purified NK cells were co-cultured with autologous dendritic cells (DCs) pulsed with one of two viral antigens, namely simian immunodeficiency virus $(SIV)_{mac239}$ Gag or HIV-1 Env, or with a control protein. NK cells were able to lyse viral antigen-pulsed DCs but not control DCs at a range of effector:target cell ratios. Furthermore, splenic NK cells of rhesus macaques infected with SIV_{mac251} were significantly more reactive to Gag-pulsed — but not unpulsed — DCs than were splenic NK cells from uninfected animals, which confirms the antigen specificity of the NK cell response. Use of blocking antibodies specific for the NK cell receptors NKG2A and NKG2C markedly reduced the ability of NK cells to lyse Gag-pulsed DCs, which is analogous to the role of the NKG2 family in memory NK cell responses in mice.

> “NK cells from macaques vaccinated 5 years previously lysed matching-antigen DCs efficiently”

In another set of experiments, rhesus macaques were vaccinated twice, 6 months apart, with a replication-incompetent adenovirus vector (Ad26) expressing HIV-1 Env or with a DNA–Ad26 prime–boost vaccine expressing SIV_{mac239} Gag. The animals were not boosted or exposed to the viruses again over the subsequent 5 years. After this period, the researchers tested how well NK cells from vaccinated animals were able to lyse DCs pulsed with the same antigen used for vaccination (the matching antigen) or with the antigen from the other vaccine (the mismatching antigen). Splenic and hepatic NK cells from macaques vaccinated 5 years previously lysed matching-antigen DCs efficiently, but had minimal reaction to mismatching-antigen DCs, which indicates the durability of the antigen-specific NK cell response.

These findings reveal the existence of memory NK cells in primates that are capable of durable antigen-specific recognition after both infection and vaccination over a period of many years. These new data add to the results of mouse studies to suggest that NK cell memory is a conserved mammalian feature, and the authors suggest that this could be exploited in the development of vaccines against HIV-1 and possibly other pathogens.

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ORIGINAL RESEARCH PAPER Reeves, R. K. *et al.* Antigen-specific NK cell memory in rhesus macaques. *Nat. Immunol.* http://dx.doi.org/10.1038/ni.3227 (2015)