IN BRIEF

ALLERGY

The absence of interleukin 9 affects neither the development of allergen-induced pulmonary inflammation nor airway hyper-reactivity.

McMillan, S. J. *et al. J. Exp. Med.* **195**, 51–57 (2002).

The T_H2-derived cytokine IL-9 has been implicated in the development of asthma. McMillan *et al.* investigated the effect of IL-9 deficiency on the development of asthma and airway hyper-reactivity (AHR) after allergen challenge. AHR and eosinophilia occurred to a similar degree in *Il9*$^{-/-}$ mice and wild-type mice, and goblet cell hyperplasia and immunoglobulin E production were also unaffected in the absence of IL-9. IL-9 is therefore not obligatory for asthma development.

T-CELL HOMEOSTASIS

Homeostatic competition between T cells revealed by conditional inactivation of the mouse *Cd4* gene.

Wang, Q. *et al. J. Exp. Med.* **194**, 1721–1730 (2002).

The role of T-cell receptor (TCR) signalling in T-cell homeostasis and post-thymic selection of naive T cells is unknown. Here, Wang *et al.* report the impairment of TCR signalling by conditionally inactivating expression of the co-receptor CD4 and the effects this has on homeostatic events. They show that T cells compete with each other during homeostatic proliferation and that T cells lacking CD4 compete poorly, indicating that the competition is based on the strength of TCR signal the cells receive.

HAEMATOPOIESIS

Identification of the earliest prethymic bipotent T/NK progenitor in murine foetal liver.

Douagi, I. *et al. Blood* **99**, 463–471 (2002).

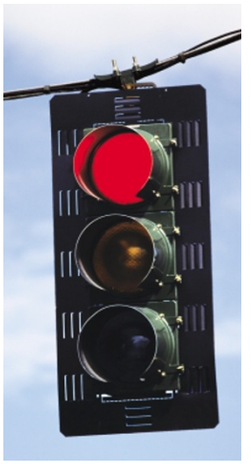
Douagi *et al.* describe the identification of a novel population of common T/NK cell progenitors (C-TNKPs) within the foetal liver. These cells are proposed to represent the immediate developmental step before migration to the thymus. This population of B220^{lo} c-kit^{+}CD19^{-} cells, which compose 0.2% of foetal liver cells, represent 70% of T-cell precursors in the foetal liver. These cells can produce both T- and NK-cell progeny at the single cell level and are present in athymic mice, indicating their prethymic origin.

IMMUNE REGULATION

IL-10-producing CD4^{+} T cells mediate tumour rejection.

Segal, B. M., Glass, D. B. & Shevach, E. M. *J. Exp. Med.* **168**, 1–4 (2002).

Although IL-10 is typically thought to have immunosuppressive functions, Segal et al. describe a pro-inflammatory population of IL-10-producing CD4^{+} T cells that mediate anti-tumour immunity. In a subcutaneous model of glioma cell growth, IL-10-producing CD4^{+} T cells that were crucial for tumour rejection were generated after vaccination with irradiated glioma cells. The cells had a cytokine profile resembling the immunoregulatory T_R1 cells that can be generated *in vivo* in the presence of IL-10.



VIRAL IMMUNITY

Stop!

Chronic infection with hepatitis C virus (HCV) is one of the main causes of liver disease, with about 170 million people infected worldwide. The mechanisms which HCV employs to promote chronic infection remain poorly understood — partly because of the lack of an *in vitro* culture system and small animal models — although active evasion of the immune response is a strong possibility. Two recent papers in the *Journal of Experimental Medicine* now show that crosslinking of CD81 by the HCV envelope protein E2 can inhibit natural killer (NK) cell function, which might affect the innate immune response to HCV and promote viral persistence.

CD81 is a member of the tetraspanin family of proteins, which are components of large molecular complexes that act as cell-surface organizers coupling different cellular functions. HCV-E2 has previously been shown to bind to the main extracellular loop of CD81. In the current studies, the functional consequences of this interaction for NK cells were investigated. Interferon-γ (IFN-γ) production in response to NK-cell stimulation by the cytokines IL-2, IL-12 or IL-15 was inhibited by crosslinking of CD81. Both groups then induced NK-cell activation by crosslinking CD16 — the low-affinity immunoglobulin G receptor (FCγRIII), which is one of the main activation receptors on NK cells. Crosslinking of CD81 on the NK cells by HCV-E2 or anti-CD81 antibodies inhibited CD16-induced tumour necrosis factor-α (TNF-α) and IFN-γ production. A similar inhibitory effect was observed for expression of the NK-cell activation marker CD25 and the release of cytotoxic granules. When the effect of CD81 crosslinking on T cells and NK cells was compared, both groups observed a co-stimulatory effect on T cells but an inhibitory effect on NK cells.

Protein phosphorylation by activated protein tyrosine kinases is an important consequence of NK-cell activation by engagement of CD16. So, what is the effect of CD81 crosslinking on these signalling events? Crotta and colleagues found that CD81 crosslinking inhibited tyrosine phosphorylation events, including the phosphorylation of CD3ζ and ERK2, specific substrates that are known to be phosphorylated following NK-cell activation.

What is the mechanism by which CD81 exerts its inhibitory function on NK cells? NK-cell activation is determined by the balance between engagement of stimulatory and inhibitory receptors. To investigate potential interactions with killer inhibitory receptors and the inhibitory signalling phosphatases SHP1 and SHP2, coimmunoprecipitation experiments were performed. No specific interaction was detected, so CD81 seems to mediate inhibition using a previously unrecognized, and as yet undefined, negative signalling pathway.

The results from these studies define an efficient HCV immune evasion strategy and show that the interaction of HCV-E2 with CD81 on NK cells provides a 'stop' signal that blocks NK-cell activation. It is likely that the ability of HCV to interfere with NK function and affect the early phase of the immune response contributes to its success at establishing chronic infections in the host.

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References and links

ORIGINAL RESEARCH PAPERS Crotta, S. *et al*. Inhibition of natural killer cells through engagement of CD81 by the major hepatitis C virus envelope protein. *J. Exp. Med.* **195**, 35–41 (2002) | Tseng, C.-T. K. & Klimpel, G. R. Binding of the hepatitis C virus envelope protein E2 to CD81 inhibits natural killer cell functions. *J. Exp. Med.* **195**, 43—49 (2002)
FURTHER READING Cohen, J. The scientific challenge of hepatitis C. *Science* **285**, 26–30 (1999)
WEB SITE
Gary Klimpel's lab: http://microbiology.utmb.edu/faculty/klimpel/homepage.htm