Journal club

SEEING THROUGH THE PARASITES' EYES

The discovery of the dichotomy between T helper 1 (T_H1) cells and T_H2 cells by Timothy Mosmann and Robert Coffman in 1986 was a major breakthrough for the understanding of how cellular and humoral immune responses are orchestrated. The next big question in the field concerned the factors that induce T_H1 cell or T_H2 cell differentiation. Two studies from the groups of Giorgio Trinchieri (Kobayashi et al., 1989) and Anne O'Garra (Fiorentino et al., 1991) were enlightening in this regard.

Kobayashi et al. reported the biochemical characterization of natural killer (NK) cell stimulatory factor (now known as IL-12), a cytokine that induces production of the T_H1 cell cytokine IFN γ by NK cells and T cells. Soon after, Fiorentino et al. showed that IL-10 antagonizes the development of T_H1 cells by suppressing the synthesis of pro-inflammatory cytokines by antigen-presenting cells (APCs). These two findings were put together by a study showing that IL-12 produced by APCs directs the differentiation of T_H1 cells and that this is inhibited by IL-10 (Hsieh et al., 1993).

Parasite infections, which cause chronic T cell stimulation, became great models to study the differentiation and functions of polarized T_H cells, as well as immunoregulatory mechanisms (Sher & Coffman, 1992). The IL-12–IFN γ axis and the antagonist IL-10 were defined as biomarkers of host resistance and susceptibility to *Leishmania major* and other infectious disease models. It became clear that IL-12 is an 'adjuvant' cytokine that drives the development of protective T cell-mediated immunity in vaccination protocols. Studies with helminths helped us to understand the basis of T_H2 cell responses and why antigen exposure through the IL-10-rich intestinal mucosa or airways is often accompanied by a T_H2 cell response. Later studies with *Toxoplasma gondii* determined that a primary role of IL-10 is to prevent excessive immune responses and consequent pathology. Today, we know that many of the functions of regulatory T (T_{reg}) cells are mediated by IL-10.

These studies had broad implications in the field of immunology. They served as a paradigm to understand how different microorganisms and tissue environments influence T_H cell differentiation, the functional diversity of CD4⁺ T cell subsets, the basis of vaccine adjuvants and the function of T_{reg} cells. These findings also had major effects on translational medicine by providing insights for clinical immunology, vaccinology and immunotherapy.

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ORIGINAL ARTICLES Kobayashi, M. et al. Identification and purification of natural killer cell stimulatory factor (NKSF), a cytokine with multiple biologic effects on human lymphocytes. *J. Exp. Med.* **170**, 827–845 (1989) | Fiorentino, D. F. et al. IL-10 acts on the antigen-presenting cell to inhibit cytokine production by Th1 cells. *J. Immunol.* **146**, 3444–3451 (1991) | Hsieh, C. S. et al. Development of TH1 CD4⁺ T cells through IL-12 produced by *Listeria*-induced macrophages. *Science* **260**, 547–549 (1993)

FURTHER READING Sher, A. & Coffman, R. L. Regulation of immunity to parasites by T cells and T cell-derived cytokines. *Annu. Rev. Immunol.* **10**, 385–409 (1992)

of certain T cell receptor chains. Consistent with an antigen-dependent mechanism, IFN γ ⁺CD8⁺ T cell expansion also required the presence of CD103⁺ intestinal dendritic cells (DCs) and their expression of MHC class Ia alleles, together suggesting that CD8⁺ T cells respond to bacterial antigens presented by intestinal DCs and proliferate owing to an IFN γ -mediated feedforward loop.

Of note, IFN γ ⁺CD8⁺ T cell numbers were increased in organs other than the gut in mice receiving the 11 bacterial strains. The authors showed that this is not due to bacterial dissemination or colonic T cell migration but may instead be due to changes in circulating metabolites induced or produced by the 11 strains.

IFN γ ⁺CD8⁺ T cells are required for the clearance of intracellular pathogens. Accordingly, mice colonized with the 11-strain mix had enhanced clearance of *Listeria monocytogenes* (both the wild-type strain and an invasive strain) compared with control mice, an effect that was markedly reduced by CD8⁺ T cell depletion.

The authors then assessed the antitumour effects of the induced IFN γ ⁺CD8⁺ T cells. Compared with control mice, mice colonized with the 11 strains had better responses in multiple tumour models with or without treatment with the checkpoint inhibitors anti-PD1 or anti-CTLA4. The therapeutic efficacy was accompanied by an increase in the number of IFN γ ⁺CD8⁺ tumour-infiltrating lymphocytes, which were enriched for cells with specificity for tumour antigens and expression of cytotoxic granzymes. Importantly, there was no evidence of colitis following treatment — a frequently observed adverse effect of checkpoint blockade.

So, this study reveals the great potential of these 11 bacterial strains, which are generally rare and low-abundance components of the gut microbiome, as therapeutics for cancer and infectious disease.

Lucy Bird

ORIGINAL ARTICLE Tanoue, T., Morita, S. et al. A defined commensal consortium elicits CD8 T cells and anti-cancer immunity. *Nature* <https://doi.org/10.1038/s41586-019-0878-z> (2019)

Following nerve crush injury, control NKp46–DTR mice were insensitive to pin-prick stimulation until around the second week post-injury. By contrast, NKp46–DTR mice in which NK cells were depleted by diphtheria toxin showed early, persistent sensitivity to pin-prick stimulation following nerve injury. Treatment of mice with an IL-2–anti-IL-2 monoclonal antibody complex to activate NK cells in vivo also reduced their sensitivity to pin-pricks following partial sciatic nerve crush injury, indicating increased axonal clearance. The authors used transmission electron microscopy to directly image axon integrity at the sciatic nerve injury site and found that injured nerves from IL-2 complex-treated mice contained more degenerated myelinated axons than control-treated mice; an effect that was lost by prior depletion of NK cells. Therefore, NK cells are important for removing damaged axons following nerve injury due to their targeted degeneration of axon fibres.

When the authors compared pain hypersensitivity in their models of sciatic nerve crush, they found that,

after axonal reinnervation, mice with a previous partial crush injury showed higher tactile hypersensitivity than mice with full nerve crush. Notably, treating mice that received a partial crush injury with IL-2 complexes increased their pain thresholds. Finally, when the RAE1 ligand was overexpressed in a population of thermal nociceptive neurons, mice showed impaired sensing of noxious heat but no changes in mechanical pain thresholds.

In summary, these findings suggest that cytotoxic NK cells are able to sense and degenerate injured sensory axons through detection of RAE1. The authors suggest that NK cells complement Wallerian degeneration to aid healthy regeneration following peripheral nerve injury. Furthermore, they suggest that targeting NK cells could possibly help alleviate pain in chronic neuropathies.

Yvonne Bordon

ORIGINAL ARTICLE Davies, A. J. et al. Natural killer cells degenerate intact sensory afferents following nerve injury. *Cell* <https://doi.org/10.1016/j.cell.2018.12.022> (2019)