Adaptive IL-21

The immune response goes through a regulated transition from the innate to the adaptive systems. In *Immunity*, Kasaian *et al.* report that IL-21, a cytokine produced by activated T cells, may limit ongoing innate immune responses. Surprisingly, IL-21R–deficient mice had normal NK cell development and full NK activation. However, IL-21 antagonized IL-15–induced growth of resting NK cells and reduced the viability of activated NK cells, yet enhanced their cytotoxicity and IFN-γ production. In terms of T cells, IL-21 blocked IL-15–driven, TCR-independent expansion of $CD44^{hi}CD8^{+}$ T cells, but enhanced proliferation and effector functions of antigen-specific T cells. Thus, IL-21 produced by activated T cells during the adaptive immune response may reduce the duration of the innate immune response by limiting NK cell activation.

Immunity **16**, 559–569 (2002)

Not-so-subtle nonself

MHC molecules direct the positive selection of TCR for self-MHC recognition during thymic development. However, a significant percentage of mature T cells also recognize nonself-MHC, resulting in allogeneic reactions. The subtle difference between syngeneic and allogeneic ligands of the TCR leading to vastly different biological responses has now been observed at the molecular level. In the *Journal of Experimental Medicine*, Luz *et al.* show that a specific amino acid mutation on the allo-MHC alters the conformation of the peptide presentation, leading to increased pMHC-TCR stability and TCRβ-pMHC contact. Thus, minimal differences in allo-MHC may lead to a global change in TCR-MHC interaction that results in a significantly different outcome.

J. Exp. Med. **195**, 1175–1186 (2002)

Targeting memory

HIV-1 infection is characterized by the progressive loss of $CD4^{+}$ T cells, but the mechanisms behind this depletion are unclear. In *Nature*, Douek and colleagues found that HIV-specific memory $CD4^{+}$ T cells contain significantly more HIV proviral DNA than other memory T cells at all stages of HIV disease. In addition, viral rebound after structured treatment interruptions correlated with an increase in HIV proviral DNA in HIV-specific memory $CD4^{+}$ T cells compared to non-HIV–specific memory $CD4^{+}$ T cells. These data provide a possible mechanism to explain the loss of HIV-specific $CD4^{+}$ T cell responses and the subsequent failure to control HIV-1 replication. The preferential infection of HIV-specific T cells could represent an evolutionary adaptation by the virus to allow survival in an otherwise immunocompetent host.

Nature **417**, 95–98 (2002)

In the skin

γδ TCR–bearing dendritic epidermal T cells (DETCs) resident in murine skin produce keratinocytes growth factors (KGFs) in response to injured keratinocytes. Because KGFs are implicated in wound healing, DTECs could play a specific role in tissue repair. In *Science*, Havren and colleagues tested the role of DTECs in wound healing using $\gamma\delta^{-/-}$ mice. Keratinocyte proliferation and re-epithelialization was slower in $\gamma\delta^{-/-}$ mice. This process was TCR-dependent, suggesting that DTECs contribute to wound repair *via* antigen recognition. Addition of DETCs or FGF-7 to skin organ cultures could restore normal wound healing in γδ DTEC–deficient skin. Thus, DETCs recognize antigen expressed by neighboring epithelial cells after injury and participate in wound healing *via* the production of KGFs.

Science **296**, 747–749 (2002)

Saved by cathepsin B

The *Leishmania* family of parasites is the etiologic agent for a variety of human diseases, including the fatal visceral leishmaniasis caused by *Leishmania donovani*. *Leishmania* parasites contain many cysteine proteases, including those belonging to the cathepsin B family, that are critical in the infection of the host. However, the mechanism of action of cathepsins in conferring survival advantage to the parasites is not known. In the *Journal of Biological Chemistry*, Somanna *et al.* isolated a cathepsin B–like gene from *L. donovani* and *L. chagasi* and show that blocking of cathepsin B activity decreases the survival of the parasites in host macrophages. Cathepsin B acts by cleaving the latent form of TGF-β into its active form. TGF-β, in turn, prevents the activation of macrophages and promotes a T_H2 response, which contributes to the survival of the parasites.

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Mucosa, too

The majority of CD1d-restricted NKT cells are sequestered to the central organs, such as the liver and spleen, and therefore their influence is thought to be mostly exerted on systemic immunity. In *Nature Medicine*, Nieuwenhuis *et al*. show that NKT cells are important in helping to clear *Pseudomonas aeruginosa* infection from the lung, the clearance of bacteria being impaired in $CD1d^{-/-}$ mice. Stimulation of NKT cells by the synthetic ligand α-galactosylceramide enhanced the clearance of bacteria *via* the induction of phagocytic activity and cytokine secretion from lung macrophages. Thus, this study revealed a relatively unexplored role of NKT cells at the mucosal surface.

Nature Med. **8**, 588–593 (2002)

Post-cleavage role for AID

AID is the only enzyme identified, thus far, as essential for antigen-driven B cell somatic hypermutation (SHM) and class-switch recombination (CSR), processes that contribute to further diversification of the immunoglobulin genes. However the exact role played by AID remains unknown. In the *Journal of Experimental Medicine*, Papavasiliou and Schatz report the generation of a mutant AID enzyme that acts as a dominant-negative molecule, interfering with the SHM process. Alteration of two key residues in AID, found within the conserved catalytic core of cytidine deaminases, caused the loss of AID deaminase activity *in vitro*. Retroviral expression of the mutant AID in the constitutively mutating Ramos cell line was sufficient to prevent SHM, but not formation of double-stranded (ds) breaks. Expression of dominant-negative AID did not cause any loss of cell viability, indicating that the dsDNA break-repair machinery is functional. These data point to a post-cleavage mutator role played by AID, either directly or in generation of the mutator.

J. Exp. Med. **195**, 1193–1198 (2002)