Filling-up

T cells undergo homeostatic proliferation in lymphopenic environments. To date, non-physiological lymphopenic environments—induced by sublethal irradiation or genetic manipulation—have been used to study this phenomenon. In *Immunity*, Paul and colleagues investigated whether the lymphopenic environment of neonates supports homeostatic proliferation. Naive CD4 T cells transferred into neonates proliferated and acquired memory cell characteristics. Proliferation was IL-7–independent and required both class II MHC–T cell receptor interactions and CD28 costimulation. The presence of both naive and memory CD4 T cells inhibited proliferation of transferred cells, whereas thymectomy enhanced cell division. V_β analysis showed that the repertoire of the responding $CD44^{hi}$ CD4 T cells was large. Thus, neonatal lymphopenia-induced proliferation is a physiological process that helps shape the immune system.

Immunity **18**, 131–140 (2003)

Tolerance is a complement

T regulatory (T_R1) cells, which suppress immune responses *via* direct cell-cell contact or though release of inhibitory cytokines, help maintain peripheral tolerance. However, little is known about the physiological conditions driving T_R1 cell differentiation. In *Nature*, Atkinson and colleagues show that cells with a T_R1 cytokine profile can be generated from human CD4 T cells by CD3 and CD46 coengagement in the presence of IL-2. These cells acquired a memory phenotype ($CD45RA^-CD45RO^+CD25^+$) and could inhibit bystander T cell activation. Stimulation of CD46 with its ligand, dimeric C3b, also induced T_R1 cell development. These data suggest that CD46 signaling induces T_R1 cell differentiation and establishes another link between complement and adaptive immunity.

Nature **421**, 388–392 (2003)

The Tolls of migrating

During an inflammatory response, polymorphonuclear leukocytes (PMNs) migrate to sites of infection, where they kill pathogenic microbes. PMN migration is regulated by chemokine receptor desensitization induced by G protein–coupled receptor kinase (GRK). In *Nature Medicine*, Fan and Malik investigated the molecular mechanism controlling chemokine receptor desensitization in PMNs. They showed that the chemokine macrophage inflammatory protein 2 (MIP-2) induced GRK2 and GRK5 expression in a phosphoinositide-3 kinase-γ–dependent manner. Lipopolysaccharide signaling, *via* TLR4, down-regulated GRK2 and GRK5 transcription in response to MIP-2. This triggered chemokine receptor desensitization, by reducing receptor internalization, and augmented PMN migration. Therefore, during infection, TLR signaling augments chemokine-induced PMN migration by modulating chemokine receptor desensitization.

Nat. Med. 18 Feb 2003 (doi: 10.1038/nm832)

Twists in NF-κB regulation

The transcription factor NF-κB has a key role in eliciting inflammatory and immune responses, thus requiring tight regulation of its activity. In *Cell*, Olson and coworkers show that NF-κB induces the expression of the basic helix-loop-helix transcription factors Twist-1 and Twist-2, which turn off the NF-κB response. Similar regulation is found in *Drosophila* between Twist and Dorsal. Twist proteins do not alter NF-κB DNA binding or stability, but can block NF-κB transactivation by forming heterodimers with RelA on the DNA target. $Twist\text{-}2^{-/-}$ mice or $Twist\text{-}1^{+/-}Twist\text{-}2^{+/-}$ compound heterozygotes died soon after birth due to cachexia induced by hyperproduction of tumor necrosis factor-α and interleukin 1β. Thus, Twist dosage is critical in regulation of NF-κB activity.

Cell **112**, 169–180 (2003)

Jak traffic control

Complex intracellular processes regulate the expression of proteins on the plasma membrane. In *The EMBO Journal*, Ragimbeau *et al*. report that Tyk2, a Jak family tyrosine kinase, regulates the surface expression of IFNAR1, a member of the type 1 interferon receptor complex, by stabilizing it on the cell surface. In the absence of Tyk2, IFNAR1 moves to the membrane, but is constitutively internalized to the endosomal compartment. Tyk2 inhibits the endocytosis and slows the degradation of IFNAR1. Tyk2 also enhances the expression of other receptor chains, such as IL-10R2. Thus, members of the Jak family may regulate cytokine responses by controlling the expression of their receptors.

EMBO J. **22**, 537–547 (2003)

IRF-4 caps Fas

Sensitivity of T cells to Fas-mediated apoptosis can be regulated by intracellular inhibitors such as FLIP or by the polarization of Fas on the surface of the cell. In the *Journal of Experimental Medicine*, Fanzo *et al*. show that interferon regulatory factor 4 (IRF-4), which is selectively expressed by lymphocytes, does not alter the expression of FLIP, but does enhance the polarization of Fas on T cells. Cells transfected with IRF-4 are more susceptible to Fas-mediated apoptosis through enhanced activation of caspase-8. Correspondingly, cells from IRF-4–deficient mice are resistant to activation-induced cell death and superantigen-mediated deletion. Thus, IRF-4 may have an unexpected role in apoptosis by regulating cytoskeletal organization.

J. Exp. Med. **197**, 303–314 (2003)

Self-selecting rules

Positive selection of developing thymocytes interacting with self-MHC on thymic epithelial cells underlies current models for how MHC-restricted T cell responses are generated. In the *Proceedings of the National Academy of Science, USA*, Martinic *et al*. show that epithelial cells of nonthymic origin are sufficient to select functional repertoires of $CD4^+$ and $CD8^+$ T cells. Tetraparental chimeric mice were generated from allogeneic embryo aggregates of thymic-deficient nude mice and either $RAG\text{-}2^{-/-}$ or *scid* mice. These mice generate efficient killer T cells and humoral immune responses upon viral challenge. As B cells from these animals express different MHC class II molecules than those expressed by thymic epithelia, any CD4 T cell help provided must originate from cells selected on nonthymic epithelial MHC. These results prompt another look at how MHC restriction shapes T cell repertoires.

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