Tumor T_{reg} cells

Regulatory T cells (T_{reg} cells) can potently suppress antitumor responses. In the *Journal of Clinical Investigation*, Mempel and colleagues track the movement and activity of T_{reg} cells and cytotoxic T lymphocytes (CTLs) in tumors to determine where and how T_{reg} cells attenuate effector responses. T_{reg} cells require both priming in the tumor-draining lymph node and exposure to antigen in the tumor microenvironment to be able to suppress CTLs. T_{reg} cells suppress CTLs in the tumor itself, and this results in the acquisition of an 'exhausted', PD-1$^+$TIM-3$^+$, functionally impaired phenotype by the CTLs. Although T_{reg} cells can interact directly with CTLs, their suppressive effect seems instead to operate via downregation of the expression of costimulatory molecules by dendritic cells (DCs), which turns the DCs into poor activators of CTLs. Therefore, T_{reg} cells alter the balance of stimulatory molecules in the tumor microenvironment to impair the effector function of CTLs. ***ZF***

J. Clin. Invest. **(19 May 2014) doi:10.1172/JCI66375**

ATP puts on the brakes

Extracellular ATP released by T cells exerts pleiotropic effects in an autocrine manner. In *The EMBO Journal*, Viola and colleagues demonstrate that paracrine ATP can also influence the motility of T cells. Activation of isolated T cells or T cells in lymph node slices via the T cell antigen receptor (TCR) shows that neighboring T cells also achieve calcium flux even without triggering via the TCR. This paracrine action is mediated by the release of ATP from the stimulated T cells, which activates the purinergic receptors P2X4 and P2X7 on bystander T cells. The calcium flux in these ATP-sensing cells results in lower motility. This ability of cells triggered via the TCR to influence the activity of bystander cells might enhance the swarming and antigen-scanning ativity of T cells in lymph nodes. *ZF*

EMBO J. (19 May 2014) doi:10.15252/embj.201386666

Transgenic APOBECs

Cytosine deaminases of the APOBEC enzyme family act as host restriction factors by targeting retroviruses. Humans express multiple APOBEC proteins, whereas mice express only APOBEC A3 (mA3A). In *PLoS Pathogens*, Stavrou *et al.* develop transgenic mA3A-deficient mice that express either human APOBEC3A (hA3A) or human APOBEC3G (hA3G) to assess the physiological antiretroviral roles of these enzymes in isolation. Transgenic mice expressing either hA3A or hA3G control retroviral infection better than wild-type or mA3A-deficient mice do; however, the mechanism differs for each. hA3G is packaged in virions in which extension cytosine deamination is evident, as is inhibition of viral reverse-transcriptase activity. In contrast, hA3A is not packaged in virions and does not inhibit viral reverse transcriptase; however, the exact mode of hA3A-mediated restriction of virus remains uncertain. Nevertheless, this system might facilitate the physiological analysis of wild-type and mutant APOBEC at various stages of retroviral infection. ***LAD***

PLoS Pathogens **(22 May 2014) doi:10.1371/journal.ppat.1004145**

Written by Laurie A. Dempsey, Zoltan Fehervari & Ioana Visan

Galectin's recognition of microbes

A diverse array of surface carbohydrate antigens can be found on resident microbes in mammalian hosts. In *Nature Chemical Biology*, Stowell *et al.* describe microbial glycan microarrays that consist of defined capsular and lipopolysaccharide antigens, which they use to investigate the recognition properties of host molecules of the innate and adaptive immune systems in serum obtained from humans, mice and rabbits. As expected, antibodies are able to specifically recognize foreign glycan moieties with relatively high affinity. Unexpectedly, several galectins show distinct specificity for self-like carbohydrate structures, including α-galactose, which allows direct recognition and killing of bacteria that express glycans containing these determinants. How galectins can mediate the killing of microbes while sparing host cells that bear similar carbohydrate moieties remains unknown; however, this innate recognition pathway helps prevent evasion of the immune response by molecular mimicry. *LAD*

Nat. Chem. Bio. **10**, 470–476 (2014)

Healthy competition

Although natural selection among cells could represent a powerful mechanism of tissue surveillance, the effects of lack of cell competition on development or disease remain unclear. In *Nature*, Rodewald and colleagues show that removing competition in the thymus by deleting the supply of bone marrow–derived progenitor cells leads to emergence of T cell acute lymphoblastic leukemia. 'Fit' competitors, such as wild-type or *Rag1*$^{-/-}$ progenitor cells, suppress the emergence of leukemia if restoration occurs within 1 week of the establishment of thymic autonomy, whereas 'unfit' competitors, such as *Il7ra*$^{-/-}$ or *Il2rg*$^{-/-}$ progenitor cells, do not. Deprivation of progenitor cells induces delays in the physiological replacement of the thymocyte compartment at CD4$^-$CD8$^-$ double-negatve stages 2 and 3 and induces the emergence of leukemia with the genomic lesions, gene-expression profiles and Notch1-activating mutations characteristic of T cell acute lymphoblastic leukemia. In addition, the data indicate that the availability of interleukin 7 (IL-7) might represent an important aspect of cell competition in the thymus. ***IV***

Nature **509, 465–470 (2014)**

Specificity control

The mechanisms that integrate the signals delivered through the TCR and cytokine receptors for the differentiation and proliferation of T cells are incompletely understood. In *Immunity*, Hodes and colleagues show that the transcriptional regulator p53 is needed to integrate IL-2-induced proliferation in the context of an antigen-specific response in both naive CD4$^+$ T cells and memory CD4$^+$ T cells. While wild-type CD4$^+$ T cells require signaling from both the TCR and IL-2 for proliferation, p53-deficient CD4$^+$ T cells undergo abundant proliferation in response to IL-2 alone. Stimulation of T cells with IL-2 in the absence of TCR signaling induces sustained p53 expression, while costimulation via the TCR terminates the initial increase in p53 protein via a decrease in p53 mRNA and induction of the ubiquitination and proteosomal degradation of p53 mediated by the E3 ubiquitin ligase Mdm2. Downregulation of p53 is required for TCR-induced proliferation, which suggests a central role for p53 in controlling antigen-specific CD4$^+$ T cell responses. *IV*

Immunity **40**, 681–691 (2014)