Regulators require CTLA-4

Mice lacking the coinhibitory molecule CTLA-4, expressed on conventional T cells after activation but constitutively on Foxp3$^+$ regulatory T (T_{reg}) cells, develop fatal multiorgan inflammation. In *Science*, Sakaguchi and colleagues show that although they survive longer than *Ctla4*$^{-/-}$ mice do, mice lacking CTLA-4 exclusively in Foxp3$^+$ cells (conditional knockout (CKO) mice) also ultimately die of autoimmunity. Foxp3$^-$ T cells from these CKO mice 'copiously produce' proinflammatory cytokines and transfer disease after injection into T cell–deficient mice. CKO mice have expanded T_{reg} cell populations, and although they develop normally in the presence of wild-type T_{reg} cells, CKO T_{reg} cells have defective suppressor activity *in vitro*. Wild-type but not CKO T_{reg} cells impair expression of the costimulatory molecules CD80 and CD86 on dendritic cells. How T_{reg} cells suppress the expression of costimulatory molecules and whether this process contributes to T_{reg} cell function *in vivo* remain to be determined. ***CB***

***Science* 322, 271–275 (2008)**

Rice innate immunity

Plants protect themselves from potential pathogens by expressing receptor kinases that function as pattern-recognition receptors to confer innate immunity. In *PLoS Biology*, Park *et al.* identify in rice a serine-threonine protein phosphastase, XB15, that regulates the activity of XA21, the innate immune receptor required for protection against *Xanthomonas oryzae*. XA21 is known to undergo autophosphorylation. XB15 interacts with XA21 to downregulate phosphorylation and activity of this receptor kinase. Loss of XB15 results in constitutive activation of genes involved in pathogen resistance and more plant death, despite enhanced resistance to xanthomona infection. Conversely, overexpression of XB15 in transgenic rice strains leads to less resistance to such infection. Pathogen recognition somehow allows XA21 to override XB15 regulation, but further work is necessary to elucidate these signals. *LAD*

PLoS Biol. **6**, 1910–1926, (2008)

Methylating Foxo

Foxo transcription factors regulate many developmental, metabolic and survival pathways. Foxo protein stability and cellular localization are regulated by the phosphatidylinositol-3-OH kinase and protein kinase B (Akt) pathways. In *Molecular Cell*, Yamagata *et al.* show that Foxo1 is methylated by the arginine methyltransferase PRMT1 at two conserved arginine residues. Such methylation blocks Akt-mediated phosphorylation, thereby stabilizing Foxo1 protein and preventing its nuclear export. Knockdown of PRMT1 leads to less Foxo1 stability, but this effect is reversed by alteration of the Akt phosphorylation site on Foxo1, which suggests that PRMT1 methylation of Foxo proteins counters regulation imposed by Akt. Notably, methylation of Foxo1 does not alter its ability to activate transcription of its target gene *Bim*. How methylation of Foxo1 influences immune cell function remains unknown. ***LAD***

***Mol. Cell* 32, 221–231 (2008)**

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Orchestrating DC functions

Studies have suggested that migratory dendritic cells (DCs) transport antigen to lymph nodes (LNs), where it is 'passed' to LN-resident DCs to mediate T cell activation. In *Immunity*, Laufer and colleagues determine that both migratory and LN-resident DCs are required for T cell activation after subcutaneous priming. Restriction of expression of major histocompatibility complex class II (MHCII) either to radioresistant epidermal Langerhans cells and dermal DCs or to LN-resident DCs shows that neither migratory DCs nor LN-resident DCs are sufficient for T cell activation. MHCII expression restored on migratory DCs in mice previously restricted in MHCII expression to LN-resident DCs restores T cell priming. Antigen processing and presentation by LN-resident DCs initiates activation and 'trapping' of T cells in LNs, whereas subsequent stimulation by migratory DCs is required for full priming. Thus, migratory and LN-resident DCs have specific functions for robust T cell activation after subcutaneous priming. *DCB*

Immunity **29**, 1–12 (2008)

Addressing gut-homing lymphocytes

Lymphocytes home to the gut because of expression of $\alpha_4\beta_7$ integrin and the chemokine receptor CCR9. In the *Journal of Experimental Medicine*, Pabst and colleagues determine that LN-resident stromal cells in mesenteric LNs (mLNs) are essential for 'instructing' the gut-homing phenotype on lymphocytes. Transplantation of peripheral LNs (pLNs) and mLNs from mice expressing enhanced green fluorescent protein into recipient host mice shows that only grafted mLNs induce $\alpha_4\beta_7$, CCR9 and gut homing on adoptively transferred T cells. Although gut-derived host DCs are present in transplanted LNs, induction of gut homing requires that stromal cells be of mLN origin. Injection of DCs into mLNs *in vivo* leads to T cell proliferation, whereas incubation of the same DCs with T cells *in vitro* does not, which again indicates stromal cell involvement. T cells upregulate CCR9 in the presence of mLN stroma cells *in vitro*, and these cells express the retinoic acid–producing enzyme RALDH2. Thus, gut tropism of T cells requires instructive signals from both DCs and LN-resident stromal cells in mLNs. ***DCB***

***J. Exp. Med.* (13 October 2008) doi:10.1084/jem.20080039**

Useful DNA breaks

During variable-(diversity)-joining recombination, developing lymphocytes temporarily have double-stranded DNA breaks (DSBs) introduced by recombination-activating gene (RAG) products. In *Nature*, Sleckman and colleagues demonstrate a previously unappreciated biological function for these DSBs. RAG-induced DSBs trigger activation of the transcription factor NF-κB, in a way partially dependent on the kinase ATM, in pre–B cells lacking elements of the nonhomologous end-joining pathway responsible for repairing RAG-induced DSBs. RAG-induced DSBs also result in the expression of over 300 genes involved in diverse processes such as cytokine signaling and lymphocyte migration. Notably, even transient RAG-induced DSBs in a nonhomologous end-joining–competent pre–B cell line activate NF-κB, and genotoxic DSBs introduced in developing B cells by ionizing radiation trigger expression of many of the genes upregulated by RAG-mediated DSBs. Whether DSBs generated by RAG proteins in lymphocytes of other lineages or maturation states facilitate distinct gene expression changes remains to be seen. *CB*

Nature (12 October 2008) doi:10.1038/nature07392