Co-opting granuloma formation

Invading mycobacteria are engulfed by macrophages, whereupon bacterial spreading is commonly thought to be restricted by the formation of immune-cell granulomas. In *Science*, Ramakrishnan and colleagues show that instead, mycobacteria co-opt this containment response by eliciting expression of matrix metalloproteinase 9 (MMP9) in neighboring epithelial cells. The bacterial protein ESAT-6, which is encoded by the mycobacterial virulence gene region RD1, is sufficient to induce MMP9 expression by epithelial cells. MMP9 expression facilitates the recruitment of more macrophages to the site of infection and perpetuates the infection cycle, thereby increasing the bacterial load in the host. Transient knockdown of MMP9 after infection leads to less granuloma formation and greater control of mycobacteria numbers. This new work reveals active involvement of epithelial cells in the generation of granulomas that thus comprise a niche permissive for mycobacteria replication and spreading. ***LAD***

***Science* 327, 466–469 (2010)**

Hang on for your life

CD44 expressed by activated T cells mediates adhesion, but whether CD44 has other physiological functions in activated T cells remains unclear. In *Immunity*, Baaten *et al.* use an influenza infection model to show that CD44 is dispensable for the migration, initial activation and population expansion of T cells but is required for the survival of T helper type 1 (T_H1) effector cells and subsequently, the generation of memory cells. In contrast to T_H2, T_H17 and $CD8^+$ T cells, T_H1 cells show greater susceptibility to Fas-induced apoptosis in the absence of CD44. The unique dependency of T_H1 cells on CD44 engagement for survival may be due to their higher Fas expression and inherent ability to rapidly assemble the death-inducing signaling complex and activate caspase-8. Preliminary data suggest CD44 mediates its protective effect by activating the phosphatidylinositol-3-OH kinase–Akt kinase pathway. *IV*

Immunity **32,** 104–115 (2010)

Sourcing S1P

Lymphocyte egress from lymph nodes is critically dependent on sphingosine 1-phosphate (S1P), whose production requires sphingosine kinase 1 (Sphk1) and Sphk2. In the *Journal of Experimental Medicine*, Cyster and colleagues identify the cellular source of S1P *in vivo*. They generate mice with conditional deletion of *Sphk2* and *Sphk1* by Cre recombinase expressed from the lymphatic endothelium locus. These mice show impaired lymphocyte egress from lymph nodes and Peyer's patches. Egress is restored by treatment with pertussis toxin to block $G\alpha_i$ protein–mediated retention signals. These mice also have altered initial lymphatic vessel morphology and junctional VE-cadherin patterning in the trachea and diaphragm. These data show that lymphatic endothelial cells are the source of S1P *in vivo* and that in addition to its involvement in lymphcyte egress, S1P may have a role in lymphatic vessel maturation. ***JDKW***

***J. Exp. Med.* 207, 17–27 (2009)**

Written by Laurie A. Dempsey, Ioana Visan & Jamie D.K. Wilson

Blunting TGF-β signaling

TGF-β triggers the phosphorylation and activation of Smad2 or Smad3 signaling adaptors, which translocate to the nucleus to regulate gene transcription. The TGF-β–Smad axis influences several key immune-cell fate-determination pathways. In *Molecular Cell*, Watanabe *et al.* identify the protein TMEPAI, encoded by transmembrane prostate androgen–induced RNA, as a feedback inhibitor of TGF-β-induced activation of Smad2 and Smad3. TGF-β signaling upregulates TMEPAI expression. TMEPAI interacts specifically with Smad2 and Smad3 via a Pro-Pro-Asp-Arg tetrapeptide and competes with the Smad adaptor protein SARA, which recruits the Smad proteins to the membrane-bound TGF-β receptor complexes. Overexpression of TMEPAI results in lower TGF-β-induced responses, whereas TMEPAI knockdown leads to enhanced Smad-dependent gene expression. How TMEPAI is regulated in immune cells remains to be elucidated. *LAD*

Mol. Cell **37**, 123–134 (2010)

Foxp3, open to regulation

Cells commit to the regulatory T cell (T_{reg} cell) lineage by upregulating the transcription factor Foxp3 in the thymus or periphery. In *Nature*, Rudensky and colleagues show that distinct conserved noncoding DNA sequence (CNS) elements at the *Foxp3* locus control the T_{reg} lineage in response to different external inputs. The CNS3 element facilitates Foxp3 expression during the generation of T_{reg} cells in the thymus and periphery, probably after binding of the transcription factor subunit c-Rel in response to signaling by the T cell antigen receptor and coreceptor CD28. CNS1 is critical for the induction of Foxp3 in peripheral naive $CD4^+$ T cells in response to stimulation by transforming growth factor-β (TGF-β). Maintenance of an active *Foxp3* locus in the progeny of dividing T_{reg} cells is dependent on recruitment of complexes of the transcription factors Foxp3-Runx1-Cbfβ to the CNS2 element after demethylation of the CNS2 GpG island. Thus, induction of a T_{reg} cell fate results from the integration of distinct cell-intrinsic and cell-extrinsic cues. ***IV***

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Biofilm-like viral structures

It has been shown that human T cell leukemia virus type 1 (HTLV-1) can be transmitted between T cells through the formation of virological synapses. In *Nature Medicine*, Thoulouze and colleagues now show that cell-to-cell transmission of HTLV-1 does not necessarily occur directly through synaptic contacts. Instead, HTLV-1-infected T lymphocytes transiently store virus particles in carbohydrate-rich extracellular assemblies on the cell surface. These extracellular virus particles are held together and attached to the plasma membrane by HTLV-induced extracellular matrix proteins, such as collagen and agrin, and cellular linker proteins, including tetherin-1 and galectin-3. These preformed transient extracellular structures that resemble bacterial biofilms rapidly adhere to the surface of target cells during contact, and removal of these structures severely compromises cell-to-cell transmission of HTLV-1. It is unclear at present whether other viruses also use biofilm-like viral assemblies to aid transmission. *JDKW*

Nat. Med. **16**, 83–89 (2009)