Broad spectrum suppressor

Lipopolysaccharide-stimulated macrophages upregulate the transcription factor ATF3, which binds to and shuts down transcription of proinflammatory genes including *Il6* and *Tnf*. In *Proceedings of the National Academy of Sciences*, Aderem and co-workers document an anti-inflammatory function for ATF3 in natural killer (NK) cells. ATF3 expression increases in the livers of mice infected with MCMV, a virus whose elimination requires NK cell production of interferon-γ (IFN-γ). NK cell–deficient mice reconstituted with ATF3-deficient NK cells show reduced MCMV loads and virus-induced liver damage, compared to those reconstituted with wild-type NK cells. After stimulation with interleukin-12 and anti-CD28, ATF3-deficient NK cells produce excessive IFN-γ mRNA but wild-type amounts of perforin and tumor necrosis factor transcripts. In contrast, ATF3 deficiency does not influence T cell IFN-γ production. ATF3 binds directly to a *cis*-regulatory element of *Ifng* in NK cells, but the molecular basis for the cell type–specific roles of ATF3 remains to be clarified. ***CB***

Proc. Natl. Acad. Sci. USA **105, 2544–2549 (2008)**

Combating tuberculosis

Previous studies have implicated natural killer (NK) cell involvement in control of mycobacterial infections. In the *Journal of Interferon & Cytokine Research*, Millman *et al.* show that human NK cells treated with *N*-acetyl cysteine (NAC) display increased control of mycobacteria. NAC leads to increased abundance of glutathione, which protects cells from oxidative damage. Monocytes infected *in vitro* with virulent *Mycobacterium tuberculosis* support less bacterial replication when cultured with NK cells, an effect that is further enhanced by addition of NAC. NK activating receptors are upregulated in response to NAC, yet infected macrophages do not seem to be directly lysed by NK cells. Increased monocyte apoptosis occurs in these cultures, but why is still puzzling, as NAC reduces the amounts of the cytokines interferon-γ, tumor necrosis factor and interleukin-10 elicited. *LAD*

J. Interferon Cytokine Res. **28**, 153–165 (2008)

CD94–NKG2D footprint

Natural killer (NK) cell recognition of human leukocyte antigen E (HLA-E) occurs through the heterodimeric receptor CD94 and NKG2A. In *Journal of Experimental Medicine*, Rossjohn and colleagues solve the crystal structure for CD94–NKG2D in complex with HLA-E and the leader peptide VMATRTLFL from HLA-G. The specificity of CD94–NKG2A for HLA-E is elucidated by comparison of CD94–NKG2A to an HLA-E–restricted T cell antigen receptor (TCR) and to ligands of homodimeric NKG2D receptor. The 'footprints' of CD94–NKG2A and the VMATRTLFL-HLA-E-restricted TCR are different: both α and β TCR chains make peptide contacts, whereas CD94 interacts much more with the peptide than does NKG2A. Also differently, hydrophobic interactions underlie the 'promiscuity' of homodimeric NKG2D for innate ligands such as MICA and ULBP3, whereas charged interactions underlie the specificity of CD94–NKG2A for HLA-E. The 'lock and key' interaction between CD94–NKG2A and HLA-E thus contrasts with the plasticity of recognition by other immune receptors. ***DCB***

J. Exp. Med. **205, 725–735 (2007)**

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Tonsil NK cells

Two types of natural killer (NK) cell in humans, $CD56^{lo}CD16^{+}$ and $CD56^{hi}CD16^{-}$, are responsible for natural cytotoxicity and/or antibody-dependent cell-mediated cytotoxicity and high production of interferon-γ (IFN-γ), respectively. In *PLOS Pathogens*, Münz and colleagues find that dendritic cells (DCs) 'matured' by stimulation with a Toll-like receptor-3 agonist or by incubation with Epstein-Barr virus (EBV) produce interleukin-12 (IL-12) in amounts that strongly activate $CD56^{hi}CD16^{-}$ NK cells. Upon such stimulation, $CD56^{hi}CD16^{-}$ NK cells, found in tonsillar tissue, produce enough IFN-γ to block B cell transformation by EBV. IFN-γ can block normal expression of the EBV protein LMP-1, which is critical for cell transformation. These data demonstrate that human DCs stimulated by EBV produce IL-12, which leads to protective IFN-γ production by tonsil-resident NK cells. Such NK cells are thus poised to protect against other pathogens that can initiate this same DC-mediated response. *DCB*

PLoS Pathog. **4**, e27 (2008)

Unique entryways

Inhibitory receptors expressed by natural killer (NK) cells face a conundrum in that these molecules must constantly interact with neighboring cells expressing cognate ligand, yet this triggers their internalization. Loss of such surface expression might therefore impair their suppressive function. In *Traffic*, Coligan and colleagues show that the inhibitory receptor CD94–NKG2A uses an unusual endocytic pathway to maintain high receptor expression at the surface. CD94–NKG2A binding to its ligand HLA-E triggers disruption of actin cytoskeleton rearrangements, which leads to inhibition of activating NK receptors. Although many endocytic pathways require actin rearrangements, CD94–NKG2A recycling does not require actin, clathrin, dynamin, protein kinase C or phosphatidylinositol-3-OH kinase. Internalization does, however, require the GTPase Rac1. CD94–NKG2A enters early endosomes but rapidly reshuttles to the cell surface, which allows this receptor to continue its inhibitory functions in the face of persistent ligation. Whether other inhibitory receptors use similar strategies remains to be determined. ***LAD***

Traffic **(21 March 2008) doi:10.1111/j.1600-0854.2008.00738.x**

Controlling cellular cross-talk

Regulatory T (T_{reg}) cell depletion elicits an increase in the proportion and number of natural killer (NK) and dendritic cells (DC) in mouse lymph nodes (LN). In the *Journal of Immunology*, Zitvogel and co-workers make progress in understanding the molecular strategies used by T_{reg} cells to regulate LN homeostasis. The DC population expansion caused by T_{reg} cell ablation is the result of CCR5-dependent recruitment of DCs to the LN. In contrast, T_{reg} cell depletion unleashes proliferation of NK cell populations already resident in LNs. Inhibited by T_{reg} cells, cross-talk between conventional $CD4^{+}$ T lymphocytes and DCs is required for production of CCR5 ligands CCL3 and CCL5—which presumably facilitate DC recruitment—and for expression of IL-15Rα on DCs—which is likely to promote NK cell proliferation. Transforming growth factor-β is required for T_{reg} cell-mediated suppression of IL-15Rα expression, but the mechanisms responsible for dampening CCR5 ligand release remain to be identified. *CB*

J. Immunol. **180**, 4679–4686 (2008)