TB targets NOS2

Control of *Mycobacterium tuberculosis* infections depends on T_H1 cell secretion of IFN-γ, which activates macrophages to elicit reactive oxidative products that can destroy infectious mycobacteria. However, virulent forms of the bacteria can persist long-term in the host and cause progressive lung disease. In the *Journal of Experimental Medicine*, North and colleagues show that virulent strains persist due to their ability to resist host production of nitric oxide. Avirulent strains of *M. tuberculosis* could be controlled without long-term lung damage in mice that lacked the respiratory burst enzymes $gp91^{Phox}$ or NOS2, showing that direct IFN-γ–mediated T_H1 immunity is sufficient protection without the additional protection of oxidative products. In contrast, NOS2-deficient, but not $gp91^{Phox}$-deficient, mice showed profound lung pathology and succumb to early death upon infection with virulent *M. tuberculosis*, despite the fact that their T_H1 responses remained intact. Thus, the ability to express nitric oxide is key to effective antimycobacterial immunity.

J. Exp. Med. **196**, 991–998 (2002)

Resisting cytokines

IFNs and TNF-α provide the first line of defense against influenza virus infection. However, two individuals lethally infected with the highly virulent avian (H5N1) influenza A virus had elevated concentrations of IFN-γ and TNF-α. In *Nature Medicine*, Webster and colleagues investigated how this strain of flu eluded the immune response despite increased cytokine production. The nonstructural (NS1) gene of H5N1 influenza viruses was associated with resistance to IFN-α and TNF-α. Pigs infected with a recombinant H1N1 influenza virus that expressed the H5N1 NS gene had higher viral titers and body temperatures and lost more weight compared to animals inoculated with H1N1 virus. Glutamic acid at position 92 of the H5N1 NS1 molecule correlated with viral resistance to cytokines, but the exact mechanism of NS1-mediated immune escape remains to be determined.

Nature Med. **8**, 950–954 (2002)

Hiding anthrax

For successful infection, *Bacillus anthracis*, the causative agent of anthrax, must evade the host immune system by killing macrophages. In *Science*, Karin and colleagues show that *B. anthracis* escapes the immune system by inducing apoptosis of activated macrophages. In activated macrophages, anthrax lethal factor inhibits p38 MAPK and triggers apoptosis by cleaving MAPKKs. The fact that NF-κB p65-deficient macrophages are also sensitive to activation-induced cell death, coupled with the requirement of p38 for the induction of certain NF-κB target genes, suggests that this MAPK may synergize with NF-κB to induce transcription of anti-apoptotic genes. Thus, *B. anthracis* paralyzes the innate immune response by inhibiting p38 MAPK activation, which converts the signal for macrophage activation to one of cell death. Selective killing of macrophages effectively shuts down secretion of chemokines and cytokines that would normally alert other arms of the immune system to the presence of this pathogen.

Science **297**, 2048–2051

Shedding decoys

NKG2D is an activating receptor expressed on NK cells, $CD8^+$ T cells and γδ T cells in humans. Experiments in mice have shown that tumors with ectopic expression of the ligands for NKG2D are rejected. However, several tumors in humans express the NKG2D ligand MIC, suggesting effective immune evasion. In *Nature*, Groh *et al.* show that tumor-infiltrating $CD8^+$ T cells, circulating T cells, NK cell and γδ T cells have reduced surface expression of NKG2D in patients with MIC-expressing tumors. Ligation of MIC results in the endocytosis of NKG2D, which is targeted to the lysosome for degradation. Down-modulation of NKG2D does not require cell-tumor contact because soluble MIC molecules are secreted by tumors into the serum. Cells with lower expression of NKG2D—as a result of exposure to MIC—are also functionally impaired, as shown by their reduced cytolytic responses and IFN-γ secretion. Thus, although MIC may promote tumor killing, the shed form allows tumors to evade the immune system.

Nature **419**, 734–738 (2002)

Evading gang

CMVs express a set of genes that are important in evading the host immune system by interfering with the MHC class I pathway. However, due to technical limitations, the three genes involved—*m04*, *m06* and *m152*—have not been studied together to understand their relative importance and their possible cooperation or antagonism. In the *Journal of Experimental Medicine*, Wagner *et al*. cloned CMV genomes as bacterial artificial chromosomes to study the result of deleting the three genes in all seven possible combinations. Infection in mice shows that these three genes are the only genes involved in the down-modulation of MHC class I expression. However, the efficacy of these genes in modulating MHC class I expression appears to be MHC allele–specific. The various virus mutants also reveal that these genes may act cooperatively—for example, *m06* and *m152*—or in an antagonistic fashion, as shown by the higher MHC class I expression when *m04* and *m152* are expressed in combination. The study of the combined effects of the three genes improves our understanding of viral evasion strategy *in vivo*.

J. Exp. Med. **196**, 805–816 (2002)

CAR crashes at cell barriers

Many viruses that infect epithelial cells use cell adhesion receptors as their entry mechanism. However, polarized expression of these receptors may actually limit their accessibility to virus particles. In *Cell*, Walters *et al*. show that adenoviruses can disrupt the tight junctions between epithelial cells; this allows viral progeny to spread throughout the infected epithelium. Adjacent epithelium cells maintain cell contacts through homotypic interactions of the CAR protein, an immunoglobulin superfamily member that also serves as the receptor for adenoviruses. However, CAR exhibits polarized basolateral expression and might block virus escape to the apical surfaces when viral progeny are shed on basolateral surfaces. But adenoviruses express the protein fiber, which competitively inhibits CAR-CAR interactions, disrupting epithelial integrity. Thus, fiber is an adenovirus virulence factor that promotes viral dissemination throughout tissues.

Cell **110**, 789–799 (2002)