**Tumor-killing DCs**

Cytotoxic T cells that are trained by dendritic cells (DCs) to recognize tumor antigens are thought to be the main artillery in an antitumor response. But Stary et al. now find that the teachers can also be dangerous. On page 1441, the authors report that DCs are also loaded with cytotoxic proteins and thus act as weapons of tumor mass destruction.

Skin tumors known as basal cell carcinomas shrink when smeared with Imiquimod, a drug that activates Toll-like receptors (TLRs) 7 and 8 on DCs. Stary et al. had previously found that mouse tumors that responded best to these drugs contained a large number of DCs. And as DCs recruit and activate T cells, the team assumed that the drug instigated the DCs to call in T cell troops.

The new study, however, shows that DCs that are activated by TLR 7/8 work by an entirely new mechanism. In human carcinomas treated with Imiquimod, two DC subsets—myeloid DCs (mDCs) and plasmacytoid DCs (pDCs)—vastly outnumbered T cells. The mDCs surrounded the tumor mass, whereas the pDCs infiltrated it. They both expressed several cytolytic molecules.

The mDCs, like natural killer cells, killed tumor cells that did not express MHC class I. The pDCs acted more like T cells and specifically destroyed antigen-positive cells in vitro. This varied target specificity implies that, together, these DCs kill all kinds of tumor cells. Imiquimod may thus be useful to treat tumors that don’t respond to T cell therapies. JEM

**Bacterial toxin cripples dendritic cells**

A mycobacterium that causes skin ulcers protects itself from the immune system by suppressing dendritic cell (DC) activity, according Coutanceau et al. (page 1395).

In the initial stages of *Mycobacterium ulcerans* infection, the skin puckers up into nodules that brim with bacteria and inflammatory cells. But this primary immune response gradually loses steam. As disease progresses, the inflammatory cells disappear and the nodules transform into festering ulcers. The bug seems to enforce immune suppression even outside the lesions as patients with ulcers have poor systemic cellular responses.

Coutanceau et al. found several structural similarities between mycolactone—a lipid toxin produced by the bug—and known immune-suppressive drugs, and postulated that the toxin might function as an immune modulator. They now find that mycolactone hinders the DCs that drive T cell activation. The toxin prevented skin-derived DCs from migrating to the draining lymph nodes and blood-derived DCs from acquiring their usual antigen-presenting and chemokine-secreting functions. But why the toxin initially allows the primary immune response to occur and how it hobbles DCs after ulcers form are still unclear.

Other mycobacteria, such as the bug that causes tuberculosis, secrete related biologically active lipids. Some of them target macrophages and inhibit the production of inflammatory cytokines, not chemokines. The team is now investigating the structural and molecular basis of this difference in toxin function. JEM

**Regulatory T cells carry new ID**

Regulatory T (T reg) cells have a new trademark and a new mode of action to go with it. While searching for a mysterious mechanism of T cell suppression, Deaglio et al. (page 1257) have also discovered a new and improved way to identify and purify T reg cells.

Some T reg cells suppress effector T cells by secreting inhibitory cytokines. But this suppression can continue even when cytokine activity is blocked, suggesting that other inhibitory mechanisms exist. Getting to the bottom of this mystery has been difficult due to the lack of cell surface markers that can be used to isolate pure populations of T reg cells for functional assays. CD25, a T reg cell surface receptor, is also expressed on activated T cells.

Foxp3, on the other hand, is unique to T reg cells, but is hidden inside them. While looking for alternate mechanisms of T reg-mediated immune suppression, the team considered two cell surface proteins—CD39 and CD73. CD39 is a surface-attached enzyme that jumpstarts the conversion of extracellular nucleotides such as ATP into AMP; AMP is further degraded by CD73 into adenosine—a known anti-inflammatory molecule that dampens T cell activation.

The team found that T reg cells from CD39-deficient mice were 50–60% less effective in inhibiting the proliferation of effector T cells in vitro and failed to prevent host T cells from rejecting skin grafts in transplantation models. CD39, which was previously not detected on T cells, was now found specifically on Foxp3+ T reg cells along with CD73. These surface proteins thus offer a simpler way to zero in on this hard-to-catch population. JEM