Dendritic cell paralysis

When airborne bacteria are inhaled into the lungs they are quickly taken up by resident dendritic cells (DCs), which ferry bacterial antigens to the lymph nodes. Once in the lymph node, DCs produce interleukin (IL)-12p70 to help activate bug-specific T helper (Th)-1 cells. According to Khader and colleagues on page 1805, DCs also use homodimers of the p40 subunit of IL-12p70 to help them embark on their journey from lung to lymph node.

The production of bioactive IL-12p70—which is composed of p40 and p35 subunits—is required for protection against Mycobacterium tuberculosis (Mtb) infection in both mice and men. Without IL-12p35 and p40, protective Th1 cells are not activated and bacterial growth goes unchecked.

Mice expressing only p40, however, fare better than those lacking both subunits, despite their inability to produce bioactive IL-12p70. This survival advantage is in part because p40 is one half of yet another Th-1–promoting cytokine (IL-23). Now, Khader et al. show that p40 homodimers also trigger the migration of Mtb-exposed DCs from the lung to the lymph nodes. This finding may help explain the observation that p40 alone is produced early and in high amounts in several models of lung inflammation, even though it blocks IL-12p70 signaling.

Only DCs that express p40 were able to respond to the chemokines CCL19 and CCL21, which normally coax DCs into the lymph nodes. DCs lacking p40 produced excess IL-10, which might explain their ambivalence to chemokines as IL-10 was recently shown to short-circuit chemokine receptor signaling in human DCs and monocytes. JEM

Melanomas disable DCs

T cells need to be activated by dendritic cells (DCs) before they will attack a tumor. Sumimoto et al. (page 1651) now show that a common skin cancer mutation interferes with this pathway, thus helping the tumor to evade the body’s immune defenses.

Activating point mutations in the serine–threonine kinase BRAF are found in 66% of all malignant melanomas. The resulting activation of BRAF-ERK-MAPK signaling—the primary pathway involved in growth factor–induced proliferation of melanocytes—immortalizes the cells.

One BRAF mutation (BRAFV600E), according to Sumimoto and colleagues, also prompts human tumor cells to produce vascular endothelial growth factor, interleukin (IL)-6 and IL-10, all of which inhibit the production of proinflammatory cytokines by dendritic cells (DCs).

Disabling DCs, and thereby preventing their activation of tumor-specific T cells, is a popular tumor cell trick. Indeed, activation of the transcription factor STAT3—common among hematopoietic and epithelial cancers—triggers the production of a similar array of DC-inhibiting cytokines. In that model, blocking STAT3 in tumor-bearing mice resulted in T cell attack on the tumor. Whether blocking BRAF will have the same reinvigorating effect on melanoma–specific T cells awaits the development of an animal model.

Interfering with BRAF signaling might enhance immune-activating antitumor therapies, such as DC immunization or T cell immunotherapy, as activation of the cells induced by these approaches might otherwise be blunted by the tumor’s suppressive output. JEM

T cells get energized

Many cell types use AMPK (AMP-activated protein kinase) to signal that energy reserves are low so more energy generation is needed. But, say Tamás et al. on page 1665, T cells also use AMPK to signal that energy will be needed in the near future, for attacking target cells, proliferating or churning out cytokines.

When cellular energy is in short supply—due, for example, to nutrient deficiency or metabolic stress—rising levels of AMP and falling levels of ATP trigger the activation of AMPK. AMPK then activates ATP-generating pathways, such as fatty acid oxidation. Tamás and colleagues now show that this pathway is also activated in T cells when their energy reserves dwindle. This is the first demonstration of physiological AMPK regulation in T cells.

But T cells turned on AMPK not only in response to falling energy levels but also in anticipation of upcoming energy needs. "If a T cell fluxes calcium," says senior author Doreen Cantrell, "it is indicating that it is about to activate and will need ATP." And this Ca²⁺ flux, they found, triggered the activation of AMPK.

Ca²⁺-induced AMPK activation required upstream Ca²⁺/calmodulin–dependent protein kinase kinases, which were not needed for AMPK activation in response to rising AMP/ATP ratios. PI3 kinase (PI3K)—an enzyme required for cytokine- and costimulation–induced energy generation in T cells—was also dispensable for AMPK activation.

Determining the importance of the AMPK pathway, relative to these other energy-boosting pathways, awaits the development of conditional AMPK-deficient mice. JEM