When confronted with potentially lethal bacterial sepsis, the brain tells the spleen to shut down the production of inflammatory cytokines, according to Huston and colleagues on page 1623. This may help explain why splenectomy renders people more prone to the immunological overreaction of septic shock when infected with certain types of bacteria.

When the brain detects inflammation or injury, it sends signals along the vagus nerve—the meandering nerve that regulates vital functions such as heart rate and digestion. This signal triggers the release of the neurotransmitter acetylcholine (Ach) from peripheral nerve endings. Ach then binds to its receptor on immune cells and inhibits the production of inflammatory cytokines, in part by inhibiting the activation of the transcription factor NF-κB. This circuit is known as the cholinergic antiinflammatory pathway.

Electrical stimulation of the vagus nerve suppresses cytokine production in several rodent models of inflammation. During bacterial sepsis, according to Huston et al., the vagus nerve’s stop signal must be delivered to the spleen, as removing the spleen or severing the branch of the vagus nerve that innervates the spleen abolished the antiinflammatory effect.

The spleen produced the bulk of the shock-inducing cytokine TNF in this model, possibly explaining why this organ had to receive the vagus nerve signal. But senior author Kevin Tracey suspects that Ach release always occurs in the spleen, even when the inflammation is happening elsewhere—a hunch they are now testing in an arthritis model. Tracey thinks that vagus nerve signals might educate white blood cells in the spleen, through which circulating cells transit every 2 to 3 min. How immune cells might translate this splenic schooling to inflammation control at distant sites remains to be determined. In the meantime, implanted pacemaker-like devices that zap the vagus nerve—used to treat seizure disorders—might also be useful for treating inflammatory diseases. JEM
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.

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.