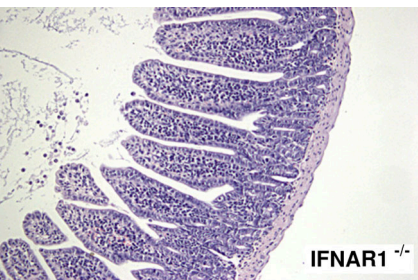
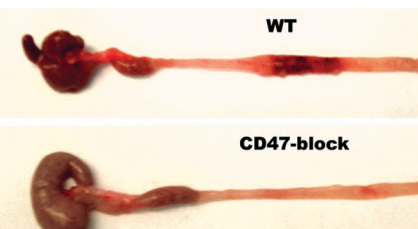


Fewer adhesion molecules (green and red) are expressed in skin vessels of elderly individuals after antigen injection.



Absence of type 1 interferons protected mice from TNF-induced tissue damage.



Treating mice with a CD47-blocker tamed intestinal inflammation.

Age-induced T cell troubles

The elderly can't fend off infections as vigorously as they once could. Agius et al. now show that part of the problem—at least in the skin—stems from memory T cells that can't get to their destination.

People have sluggish immune responses as they grow old, so it was of little surprise to Agius and colleagues that lymphocytes didn't rush to the site of antigen injection in the skin of people over 70 years old. What was surprising, however, was that T cells isolated from these individuals were not inherently defective, as they responded normally to *in vitro* activation.

Instead, it appeared that one of the first steps in the immune response fell short. After antigen injection, macrophages in elderly skin produced less TNF than did those in younger skin. Endothelial cells lining skin vessels in the elderly expressed lower levels of adhesion molecules, which are normally induced by TNF and are required for circulating T cells to migrate into tissues. As senior author Arne Akbar explains, "Road signs that direct T cells to the skin epithelium were missing."

Previous studies suggested that macrophage responses to TLR ligands wane with age, but Agius and colleagues found no such defect. Instead, suppression of TNF production might be mediated by regulatory T cells, which are known to increase with age and to inhibit TNF secretion by macrophages. Indeed, the skin of the older participants contained more of these cells, both before and after injection. Some researchers have suggested that regulatory T cells accumulate to prevent unnecessary inflammation in response to natural debris that builds up as people grow old. If this is true, speculates Akbar, relevant immune responses could also be blocked, interfering with T cell immunosurveillance and crippling responses to vaccines.

Interferin' with shock

Tumors flip out from TNF injections. Unfortunately, bodies do too. Huys et al. discover that blocking type 1 interferons (IFNs) prevents TNF-induced shock but leaves its tumor-fighting activities intact.

Type 1 IFNs, such as IFN- β , are among the hordes of cytokines, enzymes, and adhesion molecules stimulated by TNF. Although type 1 IFNs are typically associated with fighting viruses, Huys and colleagues show that these cytokines also mediate TNF-induced shock. Mice lacking IFN- β or its receptor, IFNAR-1, survived a normally lethal injection of TNF, with decreased inflammatory cytokine production and less tissue damage and cell death in the liver and bowels. These data are consistent with prior reports showing that IFN- β - and IFNAR-1-deficient mice are resistant to endotoxic shock, which is mediated largely by TNF.

Based on gene expression profiles, TNF induced a large number of genes via IFNAR-1. Among them were those encoding chemokines that attract white blood cells. Indeed, fewer leukocytes infiltrated the livers of TNF-treated mice that lacked IFNAR-1.

Type 1 interferons, however, were not required for TNF's tumor-fighting skills. With or without IFNAR-1, tumors shrank after TNF treatment—a process thought to involve cell death in the tumor vasculature. The fact that mice lacking IFNAR-1 were spared the normally toxic side effects of TNF suggests therapeutic potential. However, the risk of virus infection must be carefully assessed before interferon blockers can be used alongside TNF treatment in cancer patients.

Giving gut DCs personality

Fortin and colleagues grant a nameless group of dendritic cells (DCs) an identity and show that they promote Th17-mediated colitis.

Until now, some 40% of dendritic cells in the gut were characterized by the absence of the integrin CD103 on their surface. Here, the authors report that CD103⁻ DCs express signal regulatory protein- α (SIRP α). And unlike CD103⁺ DCs that favor the differentiation of protective regulatory T cells, SIRP α ⁺ DCs from intestinal lymph nodes promoted Th17 polarization both *in vitro* and in a mouse model of colitis. These findings are consistent with prior reports showing that CD103⁻ DCs drive the production of IL-17 from T cells. SIRP α ⁺ DCs from the spleen and bone marrow also elicited Th17 responses in culture, suggesting that the response isn't gut specific.

The generation of Th17 responses depended on the SIRP α ⁺ ligand CD47. The molecule was not required to deliver a Th17-promoting signal to the T cells, as CD47 was dispensable for

generating Th17 responses in culture. Instead, expression of CD47 on the DCs was needed for the cells to migrate to the intestinal lymph nodes where they prime T cells. SIRP α^+ cells in other parts of the body, such as Langerhans cells in the skin, similarly rely on CD47 to migrate to local lymph nodes. How CD47 drives SIRP α^+ cell migration remains unknown.

Both Th17 and Th1 responses have been reported during Crohn's disease and colitis. However, elevated levels of IL-17, IL-6, and IL-23—cytokines associated with Th17 cells—have been increasingly tied to these diseases in humans and mice.

DC–T reg cell checks and balances

Like admirable diplomats, dendritic cells (DCs) smooth out wrinkles to establish peace when conflict isn't warranted. One way these antigen-presenting cells thwart attack is by equilibrating regulatory T (T reg) cell numbers, show Darrasse-Jèze and colleagues. In addition to other processes, like triggering T cell deletion and anergy, DC maintenance of T reg cell homeostasis is a newly recognized way for DCs to maintain tolerance in the immune system.

DC and T reg cell numbers rose and fell together in mice, according to the study. When DC numbers increased in response to injection with the DC-expanding cytokine Flt3 ligand (FL), T reg cells followed suit by proliferating. Without class II MHC molecules, however, a boost in DC numbers did not trigger T reg cell proliferation, suggesting that TCR stimulation is critical for DC-induced T reg cell expansion.

Conversely, when DC numbers were decreased, as occurs in FL-deficient mice, T reg cell counts were also low. Because of this effect, mice with type I diabetes and inflammatory bowel disorder fared poorly when their DCs were depleted, as protective T reg cell numbers also dropped. The paucity of T reg cells allowed Th1 and Th17 cell numbers to rise and exacerbate inflammation, and T reg cell injections then remedied symptoms of disease.

By showing that T reg cell numbers echo fluctuations in DC numbers, the authors round out their earlier findings that T reg cell depletion increases DCs by increasing FL production. The boost in DC numbers then expanded T reg cells, according to this study. Finally, T reg cell accumulation might induce cytokines that decrease DC numbers, although this link remains speculative. This give-and-take between DCs and T reg cells likely keeps the immune system balanced to prevent autoimmunity.

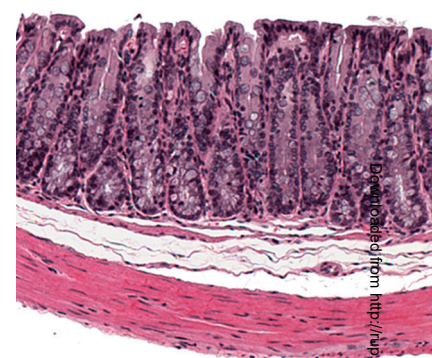
Strep's key to the brain

Meningitis sets in when certain bacteria breach the barrier protecting the brain. Uchiyama et al. now identify the key protein that *Streptococcus pneumoniae* (pneumococcus) uses to penetrate that barrier, unleashing a potentially lethal form of meningitis.

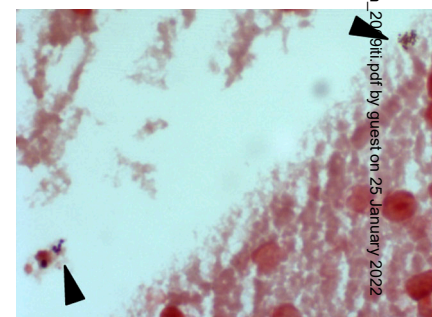
Tightly packed vascular endothelial cells lining the blood–brain barrier block most molecules from entering the cerebrospinal fluid. But certain pathogens can breach this barrier by attaching to endothelial cell receptors and riding to the other side in intracellular vacuoles. Here, Uchiyama and colleagues show that the sialic acid–cleaving surface protein, NanA, attaches the bacteria to human brain endothelial cells in culture and allows the bugs to cross the blood–brain barrier in mice. Blocking NanA prevented cell adhesion and invasion, and plugging NanA into harmless yogurt bacteria allowed these transformed microbes to invade the cultured endothelial cells. Mice infected with wild-type pneumococcus had 16 times more bacteria in their brains than mice infected with a NanA-deficient strain.

The N-terminal lectin domain of NanA bound the protein to the brain endothelial cells. When this domain was blocked or cleaved off, pneumococcus could neither adhere nor invade. The sialic acid–cleaving activity of NanA, which helps the bug colonize the nasal cavity, played only a minor role in brain invasion.

Pneumococcus has another protein called CbpA that helps the bug adhere to mucosal epithelial cells. Although this protein can also bind to brain endothelial cells, it is mostly hidden on the form of the bacterium that predominates in the bloodstream, according to the authors. Other bacteria express NanA-like proteins, therefore adding these antigens to vaccines could prove to be important in preventing various types of meningitis.



Increasing DCs triggers an increase in T reg cells and prevents colitis.



Pneumococcus (arrows) needs NanA to cross the blood–brain barrier.