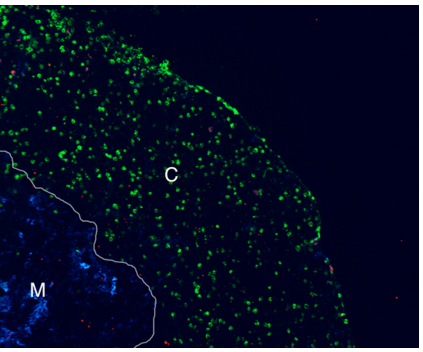


Self-reactive thymocytes (green) are deleted in the cortex (C) before reaching the medulla (M).

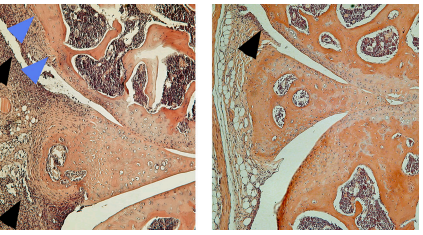
Autoimmunity fought in the cortex

In the best-case scenario, self-attacking T cells are ousted before they have a chance to leave the thymus. That essential process, which eliminates autoreactive thymocytes from the get-go, is known to occur in the thymic medulla. Now, on page 2575, McCaughtry et al. provide solid evidence that this elimination also occurs in the thymic cortex.

Although immunologists have reported T cell deletion in the cortex before, their results were made ambiguous by the transgenic mice models they used. These mice expressed T cell receptors specific for a self-peptide earlier in development than they are normally expressed. One fear was that those T cells were being deleted before they had a chance to migrate into the medulla. To quell that concern, McCaughtry's team generated a transgenic mouse in which the receptors are turned on at the appropriate time. Turns out, the earlier models were correct.

T cells reacting to ubiquitous self-antigens were deleted in the cortex alone, before entering the medulla. Furthermore, the medulla-based transcription factor AIRE, which mediates T cell deletion, did not seem to be required in the cortical deletions. Local dendritic cells, however, were needed. Without them, a large fraction of autoreactive T cell clones survived.

The locale of T cell deletion may depend on the antigen involved. Tissue-specific self-antigens are produced only in the medulla, whereas ubiquitous self-antigens, such as house-keeping peptides and the antigen recognized in the authors' mouse model, are widespread and can be handled in the cortex, at the site of first encounter. Now that the question of location has been settled, future studies can focus on learning how cortical dendritic cells control T cells gone awry.



Mice lacking DR3 (right) had decreased arthritic inflammation (black arrowheads) and bone erosion (blue arrowheads).

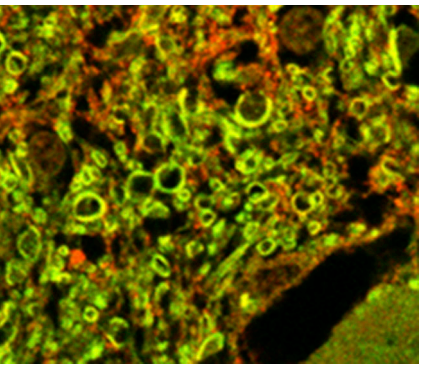
Death receptor chews up bone

Arthritis sufferers might find some relief in a new compound found to ease bone damage in mice. Bull et al. (page 2457) prevented joint erosion when they crippled a member of the TNF receptor superfamily, Death Receptor 3 (DR3), by blocking its ligand, TL1A.

Patients with rheumatoid arthritis are more likely to have extra copies of the gene that codes for DR3. A causative role for DR3 in disease pathology, however, had not been shown. Bull et al. now find that mice lacking DR3 are freed from the bone damage usually caused by antigen-induced arthritis. And blocking TL1A curtailed the bone erosion typical of collagen-induced arthritis in mice.

Back in the dish, the team investigated how this receptor–ligand pair might induce bone destruction in humans. They found that the addition of TL1A to ordinary monocytes from human blood enhanced the generation of bone-resorbing osteoclasts. Although how TL1A leads to osteoclast differentiation is not yet clear, its DR3 receptor is known to activate NFκB, which is required for osteoclast formation.

A few stones remain unturned in the hunt for vandals, as obstructing TL1A didn't eliminate bone destruction altogether. Still, the researchers point out that the anti-TL1A antibody did ameliorate much of the damage.



Aquaporin-4 (red) and EAAT2 (green) colocalize in normal spine.

Pain in the brain

A severe and unusual disorder often confused with multiple sclerosis (MS) has now become a little less mysterious. On page 2473, Hinson and colleagues demonstrate how the disease's distinguishing autoantibody disrupts glutamate regulation.

Neuromyelitis optica (NMO), also known as Devic's disease, results in MS-like lesions in the optic nerves and along the spine. Yet unlike MS, NMO is associated with production of a specific autoantibody known as NMO-IgG. Clinicians use NMO-IgG to diagnose the disease, but they don't know how the antibody contributes to its symptoms—sight impairment, paraplegia, and loss of limb, bladder, and bowel sensation.

In 2005, the same group identified NMO-IgG's target as aquaporin-4, a water channel protein concentrated in astrocyte membranes along the blood-brain barrier. However, the finding was somewhat perplexing because myelin damage occurs on nerve cells, not on astrocytes. Now the team confirms that astrocytes are indeed the relevant target, and show how autoantibody binding can lead to demyelination. Clue: when astrocytes hurt, their duties lapse, too.

When NMO-IgG binds to aquaporin-4, they show, the levels of the astrocyte glutamate transporter EAAT2 drop. And no transporter, no glutamate regulation. Astrocytes themselves aren't sensitive to changes in glutamate levels, but neurons and oligodendrocytes are. These cells rely on

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EAAT2 to mop up excess glutamate from extracellular space. Accumulation of the neurotransmitter can be toxic to myelin-making oligodendrocytes.

After spelling out the pathway in astrocyte in vitro assays, the team examined human tissue. Sure enough, NMO lesions along cadaver spines lacked both aquaporin-4 and EAAT2. Lesions from MS patients show no such deficiencies, highlighting another way in which the demyelinating disorders differ.

If the groups' results are confirmed in vivo, drug development could be straightforward. Therapeutic trials for glutamate antagonists, created to treat other neurodegenerative diseases like Lou Gehrig's disease (or ALS), are already underway.

Friend to the brain, foe to the spine

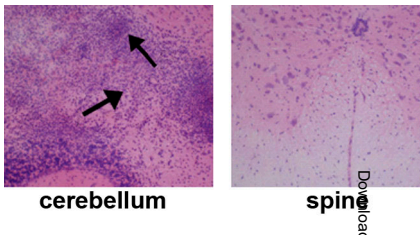
Shouting during a World Cup match and shouting during a funeral will be met with different reactions. Context is equally important in a cytokine outburst, find Lees et al. on page 2633. Regional responses to interferon-γ (IFNγ) dictated whether the spinal cord or cerebellum came under fire in mice with EAE, a mouse model of human multiple sclerosis (MS). In other words, both outburst and audience matter.

IFNγ, the signature T helper (Th)-1 cytokine, contributes to CNS inflammation during EAE. But not all forms of EAE are alike. In classical EAE, the T cell attack is focused on the spinal cord. But in atypical disease, the cerebellum and brain stem are the primary victims. A prior study suggested that the ratio of interleukin (IL)-17 to IFNγ determines whether disease pathology occurs in the spine or brain, with increasing levels of IL-17 associated with disease in the brain. But the data from Lees et al. instead show that lesion location is mainly controlled by the brain's response to IFNγ.

When transferred into wild-type mice, the authors show, myelin-specific Th1 cells attacked the spinal cord. But when transferred into mice lacking the IFNγ receptor, the cells instead attacked the cerebellum and brain stem, sparing the spinal cord. The production of IL-17 by the transferred T cells was comparable in both settings. However, the production of IL-17 by non-T cells predominated in the cerebellum, suggesting that IL-17–producing cells contribute to atypical disease but do not determine its location.

In agreement with past reports, however, transferring mixed populations of IFNγ- and IL-17–producing cells resulted in a mixed disease phenotype, with increasing numbers of IFNγ producers causing progressively more spinal cord disease.

Why IFNγ induces inflammation in one tissue and not another remains unknown—particularly because no obvious regional differences in the expression of the receptor were detected. The authors suspect that IFNγ triggers a localized production of T cell–attracting chemokines in the spine.



Inflammation (arrows) is focused on the cerebellum, not the spine, in mice lacking the IFNγ receptor.

Giving imatinib a hand

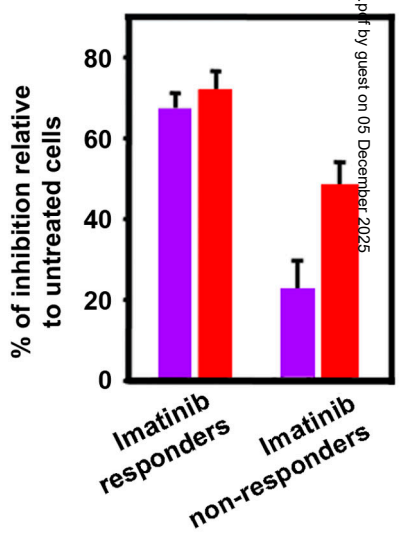
Researchers have discovered a new a way to make the anticancer drug imatinib more effective. By suppressing the oncogene *AHI-1*, Zhou and colleagues were able to hold chronic myeloid leukemia (CML) in check (page 2657).

Imatinib is currently the most popular targeted therapy for CML. The leukemia is associated with the abnormal fusion of *BCR* with a kinase gene, *ABL*, which results in a perpetually active kinase known as BCR-ABL. Imatinib, a tyrosine kinase inhibitor, slows down the spread of cancer by blocking BCR-ABL activity. But the drug doesn't work in everyone and patients often relapse, most likely because the drug only targets mature cells, leaving CML stem cells behind. Scientists have therefore been hunting for complementary therapies that act on pathways left undeterred by kinase inhibitors.

Mutated versions of the recently identified protein AHI-1, whose function is unknown, have been shown to be highly expressed in leukemic stem cells—the same cells that express BCR-ABL in patients with CML. Here, Zhou et al. show that expressing AHI-1 in stem cells turns the cells cancerous in vitro, and these cells caused lethal leukemia when transferred into mice. When expressed in BCR-ABL–positive cells, AH1-1 exacerbated the growth-promoting effects of the fusion protein.

AHI-1's growth-promoting activity was attributed to the ability of AHI-1 to bind to BCR-ABL, along with an activated version of the downstream signaling protein JAK2. Cells expressing this complex were resistant to the kinase-blocking action of imatinib. Indeed, blocking AHI-1 in cells from imatinib-resistant CML patients restored the cells' sensitivity to the drug.

With this finding, the race is on to find a drug to block AH1-1. As other studies have recently suggested, the cure for CML and other leukemias may not lie in a miracle drug, but rather in a carefully concocted cocktail of targeted therapies.



A combination of imatinib and an AHI-1 blocker (red) killed more cells from imatinib-resistant CML patients than did imatinib alone (purple).