Raising more than just hope for cancer treatment

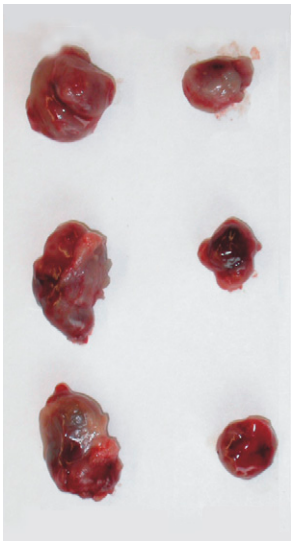
Bedroom performance-boosting Viagra also boosts the immune system's battle against cancer, report Serafini et al on page 2691.

In cancer patients, though the body generates tumor-specific antibodies, their efficacy is neutralized by the tumor itself. Tumors recruit cells such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells, which suppress the body's immune system, thus allowing the tumors to escape immune recognition. Borrello's team has been investigating ways to overcome this immunosuppression.

Suppression of T cells by MDSCs requires, among other things, nitric oxide production. The team reasoned, therefore, that reducing nitric oxide levels might boost immunity in cancer patients. They thus turned to Viagra. Besides its well-known vasodilatory effect, Viagra also reduces nitric oxide production through a separate but linked pathway.

The team gave Viagra to mice with colon carcinoma and found that the immune systems of the mice were indeed boosted. The mice had an increased number of cytotoxic T cells, and tumor outgrowth was reduced by 50–70%. Viagra also provided a boost to T cells transferred to the mice using adoptive cell therapy, with tumor growth being reduced still further.

Viagra, either alone or in conjunction with transferred T cells, did not eradicate the tumors but did significantly slow their progression. Eradication would require a full understanding of the multiple, complex pathways that lead to tumor-induced immunosuppression. In the meantime, the immediate availability of Viagra means its potential clinical use can be readily tested. JEM



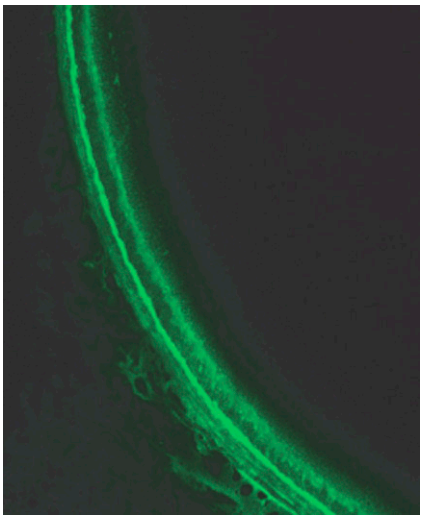
Tumor size in mice is reduced by Viagra treatments (right).

Me, myself, and eye

The lack of just one self-antigen in the thymus can launch a tissue-specific autoimmune attack, report DeVoss et al. (page 2727).

T cells are taught which antigens to ignore as they develop in the thymus. Those whose antigen receptors recognize self-proteins are normally eliminated, preventing them from escaping into the circulation and later attacking self-tissues. The transcription factor Aire (autoimmune regulator) drives the expression of many tissue-specific antigens in the thymus; without Aire, mice develop a panoply of autoimmune diseases. But so far no studies have proven the link between defects in Aire-induced expression of tissue antigens in the thymus and the development of autoimmunity against those tissues.

The team showed that one of the problems that crops up in *aire*$^{-/-}$ mice—a spontaneous autoimmunity of the eye—is due to a T cell attack on an eye-specific interphotoreceptor retinoid binding protein (IRBP). IRBP, the authors found, was expressed at a low level in the wild-type thymus, but was missing in the *aire*$^{-/-}$ thymus. Wild-type mice transplanted with thymi lacking IRBP developed the same eye disease, proving that the lack of thymic IRBP was solely responsible for the disorder.



The lack of thymic IRBP creates autoantibodies (green) against retinal IRBP.

Humans lacking Aire also develop retinopathy, although they more commonly develop other organ-specific autoimmune diseases. Given that *aire*$^{-/-}$ mice develop a range of tissue-specific autoimmune disorders, the authors plan to test whether those that are common to humans can also be pinned on the loss of a single antigen. JEM

IRF3 balances killing and cleaning

A clean house is a sign of a boring life. When more interesting or urgent matters arise, the housework has to wait. Similarly, when the body needs to fight infection, the liver's clean-up work is impaired. Chow et al. (page 2589) now show why: switching on virus-fighting factor interferon also switches off the liver's detoxification pathway.

Viral infection can cause metabolic disorders, including cholesterol and bone metabolism defects as well as Reye's syndrome, a defect in which aspirin becomes toxic because the liver fails to break it down. Liver detoxification is partly regulated by a transcription factor called retinoid X receptor (RXR), which turns on drug metabolism genes. But RXR is turned off by viral infection, Chow and colleagues now find.

RXR gets down-regulated by interferon regulatory factor 3 (IRF3), the same factor responsible for promoting virus-killing interferon expression as part of the primary immune response.

The team's work reveals a mechanism for crosstalk between immunity and metabolism—but why might cells need such crosstalk? "Fighting infection costs energy, and so does metabolism," explains Chow. The simultaneous switching of resources in favor of the immune response and away from metabolism might thus be the body's way of balancing the energy budget. JEM

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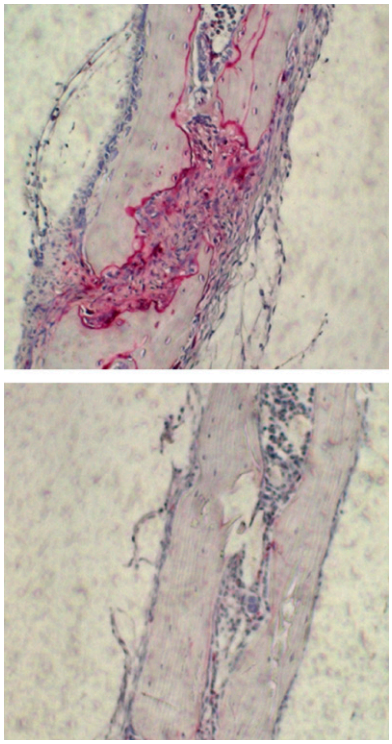


Bone destroying cells (red) flourish in the presence (top) of the IL-17 cytokine.

Bone destruction by Th17

T cells that produce cytokine IL-17 activate bone-destroying osteoclasts, report Sato et al. on page 2673. The finding pinpoints a potentially powerful target for autoimmine arthritis therapy.

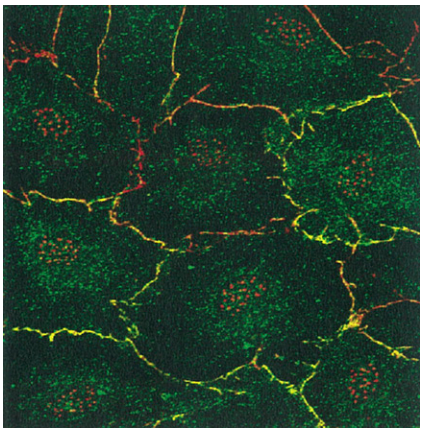
Autoimmune arthritis, such as rheumatoid arthritis, is a T cell–driven disease, in which bones are destroyed by hyperactive bone-resorbing osteoclasts. Activated T cells have long been implicated in arthritic inflammation and the resulting bone destruction, but exactly which type of T cell is responsible has never been confirmed. T helper (Th)-1 cells, the cells that promote cellular immunity, have received the lion's share of the blame. Yet Th1's signature cytokine, IFNγ, actually inhibits bone resorption by osteoclasts.

The study by Sato et al. helps resolve this paradox by putting the blame for inflammatory bone destruction on a recently described T cell subset called Th17. Th17 cells, named for their propensity to secrete the cytokine IL-17, have also been implicated in other models of autoimmune inflammation.

The team tested whether various T cell subsets—Th17, Th1, Th2, and regulatory T cells—affected osteoclasts. They found that only Th17 cells enhanced osteoclast differentiation—a prerequisite for bone resorption. IL-17 itself also promoted osteoclast differentiation. The induction of osteoclast differentiation was only seen when bone-forming osteoblast cells were also present in the culture. Osteoblasts provide osteoclasts with differentiation signals; thus it now appears that IL-17 might prompt the osteoblasts to release these signals.

Current treatments for autoimmune arthritis reduce inflammation by using broad-based immunosuppression. The identification of both the specific T cell subset and the cytokine responsible for promoting bone resorption might lead to a more powerful therapy that also targets skeletal damage. JEM

Reducing cell–cell stickiness with JAM-C



JAM-C (green) loosens cell junctions (red) to increase blood vessel permeability.

Most cell junction proteins increase endothelial cell–cell adhesion. But junction adhesion molecule-C (JAM-C), despite its sticky name, loosens vascular endothelial cell connections, thus allowing increased blood vessel permeability.

Increasing the permeability of small blood vessels is essential for new vessels to form and for leukocytes to escape the circulation and enter surrounding tissues during inflammation and tissue repair. Permeability is thought to be controlled by tight junctions between neighboring cells. Most tight junction components promote cell–cell adhesion and thus reduce permeability. But Orlova et al. (page 2703) show that the tight junction protein JAM-C does the opposite—it promotes permeability. Indeed JAM-C is the first junctional molecule reported to behave this way.

Using dye tracking, the team showed that knocking down JAM-C reduced endothelial permeability both in vitro and in vivo. The permeability-promoting effect of JAM-C was not on tight junctions themselves, but rather on a different type of cell–cell junction called adherens junctions, which contain the adhesion protein VE-cadherin. Knocking down JAM-C led to increased adhesion between VE-cadherin molecules at cell junctions. Such increased interaction is thought to trigger, via junction-associated factors, a series of steps that ultimately promotes actin depolymerization—thus further reducing permeability, as cells are unable to contract and pull apart. Consistent with this theory, knocking down JAM-C also reduced intracellular actin polymerization.

That a molecule from one type of junction can promote permeability by acting on another type of junction was surprising. The team found, however, that JAM-C increased endothelium permeability whether located at the cell junctions or diffusely distributed in the cytoplasm, indicating that JAM-C might be a signaling as well as structural protein, though the authors have yet to investigate this possibility.

One of the many more typical tight junction molecules that reduce vessel permeability is JAM-A, a closely related family member of JAM-C. How two such structurally similar junction molecules can have opposing effects on blood vessel permeability remains to be determined. JEM