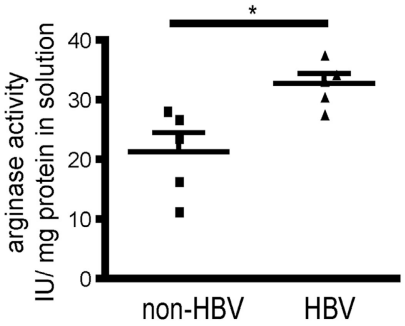


The arginine-destroying enzyme arginase is elevated in the livers of patients with chronic hepatitis B virus infections.

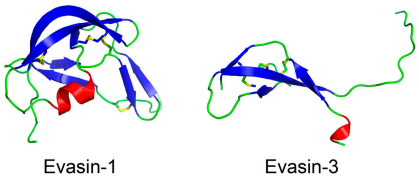
Arginine reverses T cell defects

An amino acid might help fight chronic hepatitis, according to a study by Das et al. (page 2111).

The amino acid arginine is indispensible for the host's T cell response against tumors or chronic infection. Without arginine, a T cell receptor (TCR) component cannot be produced efficiently, thus dampening TCR signaling. As a result, the cells do not proliferate normally or produce the survival cytokine IL-2, although they still make inflammatory cytokines such as IFNγ and TNF.

Das et al. now find that $CD8^+$ T cells in the livers of patients with chronic hepatitis B infections show signs of arginine starvation. Despite proliferating poorly, the cells' production of IFNγ and TNF might explain the liver damage seen in these patients. The amino acid deficiency stemmed from the activity of the arginine-destroying enzyme arginase, which was elevated in inflamed livers. The arginase source is still unknown but seems to be confined to the liver, as T cells elsewhere in the patients were less affected.

Culturing patients' liver-derived $CD8^+$ T cells with arginine corrected their defects. Whether arginine supplements can help cure hepatitis B remains to be seen.



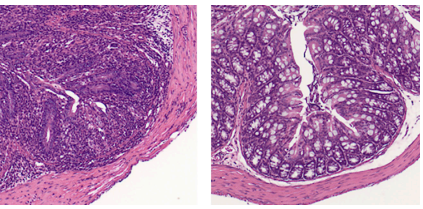
Ticks secrete several different evasins, each of which blocks a different chemokine.

Ticks' evasion cocktail

On page 2019, Déruaz et al. find that ticks might prefer to take on immune cells one at a time rather than brave the whole lot at once.

Some worms and viruses fend off immune cells by neutralizing the chemokines that attract them. These species make one chemokine-blocking protein that covers all the bases. But ticks don't use this one-for-all strategy, the authors now find. Instead, they made at least three single-chemokine blockers, which probably prevent host immune cells from swarming into the bite site and clogging up the ticks' food pipeline. These anti-chemokines, called evasins, each had a unique shape that might contribute to their selectivity.

Ticks might have evolved this selectivity to counter the host's step-wise immune response to the Lyme disease parasite they carry. In parasite-infected hosts, neutrophils usually arrive first to the bite site, followed by eosinophils and monocytes, and finally other immune cells. Tick saliva has different anti-chemokine activity at different times during feeding, suggesting that having several evasins might somehow better counter this staggered cell influx. Viruses, on the other hand, do not have the luxury of combating one cell type at a time and might therefore depend on a single multi-purpose protein.



Naïve-turned-suppressor cells dampen colitis (left).

Spreading tolerance by converting

Unlike some religious leaders, suppressive T cells need more than just charisma to spread messages of tolerance: the cells rely on a cell surface cytokine complex to convert others, according to Andersson et al. (page 1975).

Regulatory T (T reg) cells suppress other T cells in part via the cytokine TGF-β, which can convert naïve $CD4^+$ T cells into suppressor cells. Andersson et al. now find that naïve $CD4^+$ T cells turn into suppressor cells only when they bump into T reg cells that have an inactive TGF-β complex on their surface. Proteolysis of the inactive complex, which liberates soluble protein, was required for conversion. Inhibiting the protease or swamping the cells with inactive complex prevented cleavage and thus conversion. The converted cells could suppress gut inflammation when transferred into mice suffering from colitis.

Other immune cells also secrete soluble TGF-β, but they do not seem to force conversion—at least in this system. Previous experiments showed that naïve T cells cultured with T reg cell–depleted spleen cells, which secrete TGFβ, fail to convert. Non-T reg cells don't express the inactive surface complex, so perhaps its cleavage is needed to trigger other conversion-supporting signals.

The latent TGF-β complex was present only on T reg cells that had been stimulated via their T cell receptors. This specificity might allow T reg cells to limit conversion by delivering the TGF-β signal only to T cells bound to the same antigen-presenting cell and thus on the verge of being activated. "We wouldn't want T reg cells to run amok and convert all naïve T cells," says lead author Ethan Shevach. How often T reg cells rely on this mechanism and its impact on the induction of tolerance in vivo are unknown.

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Chemical makeover inhibits IL-8

On page 2085, Proost et al. find that altering a single arginine turns an inflammatory chemokine docile.

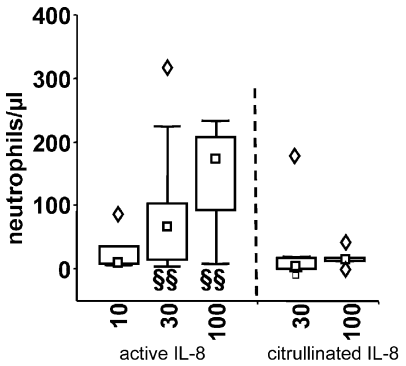
The chemokine IL-8, which activates and recruits neutrophils, is secreted as a mixture of isoforms that vary in length due to proteolysis. A cut after the first five amino end residues produces active protein, whereas cuts elsewhere inhibit activity. Proteolysis might thus be one way to control the amount of active IL-8, but it's not the only one, as Proost et al. now find. The transformation of a single arginine into the nonessential amino acid citrulline also shuts it down.

Among the IL-8 isoforms secreted by activated human immune cells, one lacked the arginine adjacent to the activating cleavage site. The lack of mutations in this isoform suggested that the alteration was post-translational, and the protein had not been trimmed, suggesting that the arginine had been replaced rather than cleaved off. The alteration did not change the isoform's mass, hinting that the replacement residue might be citrulline, which is similar in mass to arginine. Indeed, the authors found citrulline in arginine's place.

Citrulline-containing IL-8 did not efficiently activate the IL-8 receptor on neutrophils, as it resisted the activating proteolysis. It also bound poorly to sugar groups that help tether neutrophils to blood vessels. When injected into mice, this isoform thus failed to draw neutrophils to the injection site.

This modified isoform accounted for only a small fraction of the total IL-8 produced by activated cells in culture. Whether cells produce more of this isoform in vivo is not yet known. The authors have also yet to determine whether the isoform's production increases during inflammation. The enzyme that turns arginine into citrulline, peptidylarginine deiminase (PAD), is secreted mostly by monocytes, which follow neutrophils into inflamed sites. Monocytes might turn up PAD production to limit the entry of more neutrophils and prevent excessive inflammation.

PAD also citrullinated a few other chemokines, but whether these modifications are similarly inhibitory remains to be seen.



A citrulline-containing IL-8 isoform fails to recruit neutrophils.

Large tumors too slippery for T cells?

On page 2125, Quezada et al. find that big tumors might evade T cell destruction by shutting down adhesion molecules.

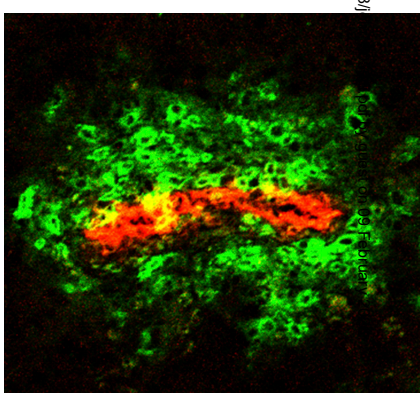
Tumor-fighting T cells work better when suppressive regulatory T (T reg) cells are not lurking. But treatments that either deplete T reg cells or boost anti-tumor T cell activity aren't enough to destroy tumors, as Quezada et al. now show.

As seen in other tumor models, skin tumors in mice were destroyed when the group depleted T reg cells before tumor implantation. But if they depleted T reg cells after tumors had already developed, the treatment failed, even if the animals were given T cell–boosting drugs. Plenty of potential tumor-killing T cells were available, but they did not seem to infiltrate the tumors.

Small tumors, at least, were sensitive to T cells. When T reg cell depletion was combined with T cell–boosting drugs, small, newly implanted tumors were destroyed. But well-established tumors resisted the effects of this regimen.

Established tumors, the group found, had fewer adhesion molecules on surrounding blood vessels. To determine whether these adhesives might help T cells invade bigger tumors, the group induced adhesion molecules in mice using irradiation. Zapped mice that were then injected with anti-tumor T cells along with activity-enhancing drugs fought off tumors. But irradiated mice that were also injected with T reg cells put up a weak fight. How tumors dial down adhesion molecules as they grow and whether T reg cells coerce them into doing so remain to be seen.

The findings might explain why treatments that deplete T reg cells and enhance killer T cell activity haven't fared well in clinical trials. Perhaps combining them with irradiation might make them more effective.



Boosting adhesion molecule expression in tumor blood vessels (red) allows more tumor-killing T cells (green) to gain access.