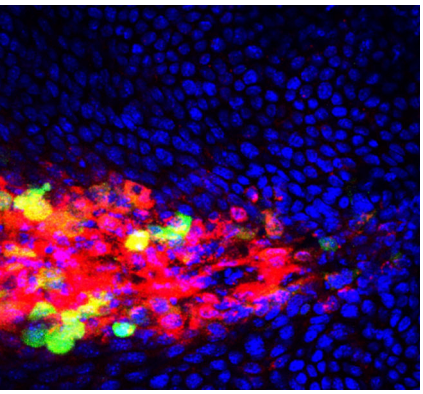


HSV-1 (red) promotes VEGF-A expression (green) by infected corneal epithelial cells.

How herpes launches lymphatics

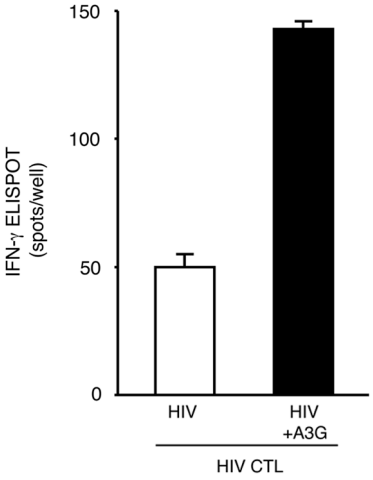
Herpes simplex virus 1 (HSV-1) provokes lymph vessel overgrowth in the eye by triggering an unexpected growth factor, report Wuest and Carr. And this cascade could be blinding.

Although HSV-1 infects 50–90% of people worldwide, it rarely causes substantial harm. Occasionally, however, the virus sneaks into the cornea during periods of reactivation, obscuring vision or causing blindness. The inflammatory response provoked by the infection includes new blood vessel growth, which may be partly to blame for the resulting eye damage. Clinical evidence suggests that new lymph vessels may also appear during HSV-1 eye infections.

VEGF growth factors drive inflammatory lymph vessel growth in other situations, such as wound healing and bacterial infection. In these situations, infiltrating macrophages secrete VEGF-C and -D, which bind to the VEGFR-3 receptor to trigger new lymph vessels. Here, Wuest and Carr find that HSV-1 induces lymph vessel growth without help from macrophages or the usual VEGF middlemen.

Instead, HSV-1–infected epithelial cells drove vessel growth by secreting VEGF-A. The new lymph vessels persisted after viral replication ceased and also remained functional, as soluble antigens drained from the cornea into the draining lymph nodes.

Blossoming vessels could escalate inflammation by allowing antigens access to draining lymph nodes. Nevertheless, HSV-1 may be wise to exploit VEGF-A. The factor blocks dendritic cell maturation, perhaps helping the virus to evade the ensuing immune attack.



A3G enhances activation of IFN-γ–producing, HIV-specific CTLs.

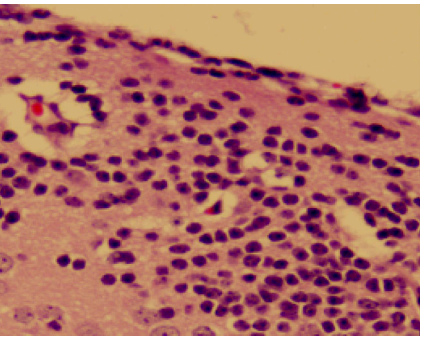
Two-pronged attack on HIV

The antiretroviral factor A3G does more than mutate HIV, report Casartelli and colleagues. It hastens the deployment of cytotoxic T cells.

A3G (short for APOBEC3G) is a restriction enzyme that inhibits HIV replication by introducing mutations into the viral genome. The team found that this editing strengthens the HIV-specific cytotoxic T lymphocyte (CTL) response. When HIV-infected cells expressed A3G, truncated viral peptides were loaded onto MHC class I machinery and were efficiently presented to HIV-specific $CD8^+$ T cells. Wild-type HIV strains elicited a weaker response than strains missing their A3G-degrading weapon, the protein Vif. Although interferons in the innate arm of the immune system set off A3G, the authors show that the protein's enzymatic activity is critical for optimizing adaptive immunity.

To explain why imperfect viral peptides enhanced cytotoxic T cell activity, the authors invoked the controversial DRiP (defective ribosomal products) hypothesis, which predicts that most antigenic peptides originate from truncated proteins that degrade rapidly and enter into the MHC class I antigen–processing pathway. In fact, HIV made to artificially express severed Gag proteins, like those altered by A3G, enhanced $CD8^+$ T cell activation.

The control A3G has over HIV may help account for why the disease does not affect people equally. It's possible that elite controllers—HIV-infected individuals who successfully suppress the virus—may have an A3G polymorphism to thank. However, the correlation between their polymorphisms and their CTL response has yet to be investigated.



Brains from progranulin-deficient mice become abnormally inflamed in response to infection.

Dementia's inflammatory link

Inflamed brains pose a danger to themselves, according to a report by Yin and colleagues that identifies a potential link between the immune system and neurodegenerative disease.

Mutations that diminish expression of the protein progranulin cause frontotemporal dementia in humans. Progranulin is involved in various processes, including inflammation suppression, wound healing, embryonic development, and tumorigenesis. But its role in dementia has remained mysterious. Here, Yin et al. show that progranulin may prevent brain cell damage in part by promoting the expression of the anti-inflammatory cytokine IL-10.

In response to *Listeria* infection, mice that lacked progranulin produced little IL-10 and lots of inflammatory cytokines, including the monocyte chemoattractant MCP-1. Yet despite the elevated response, fewer monocytes were deployed to infected sites, and the mice eventually succumbed to infection. Senior author Aihao Ding explains these counterintuitive results by saying that if alarms were blaring everywhere, police (i.e., monocytes and other leukocytes) wouldn't know where to head.

Text by Amy Maxmen
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Microglia, the macrophages of the brain, echoed the body's inflammation in the absence of progranulin. The exaggerated inflammatory response of activated, progranulin-deficient microglia helped trigger neuronal death. Without progranulin, neurons were vulnerable to stresses like oxygen and glucose deprivation—conditions that might occur during a concussion or stroke.

The team's mice never developed the brain atrophy characteristic of patients with frontotemporal dementia. But they did share some features. Levels of ubiquitin and the phosphorylated version of the protein TDP-43 were abnormally high in certain brain regions in the progranulin-deficient mice, indicating some similarity to the ubiquitin- and TDP-43–rich scars that dementia patients acquire. The authors are now investigating whether their mice develop dementia-like behavioral changes.

δ-Catenin aids angiogenesis

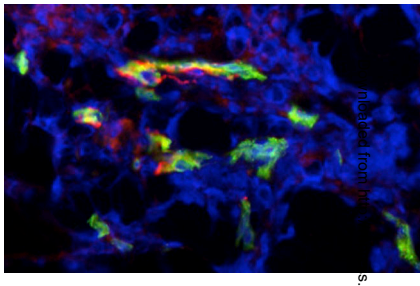
By lessening the level of a protein, DeBusk et al. bring pathological angiogenesis to a halt.

Formerly known for its effects on neuronal growth, the protein δ-catenin is now found to be highly expressed in human vascular endothelial cells where it assists vessel growth. Although this is the first report of δ-catenin in vessels, other proteins are known to function in both vascular and neuronal networks, which grow side-by-side in the developing embryo. In vessels, δ-catenin acted as it does in neurons, assisting cell motility by activating Rho GTPases.

Vessels grew normally in the healthy tissues of mice that lacked one or both of the δ-catenin–encoding alleles. The resulting paucity of δ-catenin disrupted only vessel growth associated with tumors and healing wounds. Inflammation, which often coincides with cancer, triggered δ-catenin through the transcriptional regulator NF-κB. In samples from patients with lung cancer, the team found that tumors expressed more δ-catenin than did the surrounding tissue.

Children bearing defects in one δ-catenin allele acquire a lethal disorder, Cri-du-chat syndrome, which is characterized by neuronal, developmental, and heart defects. Before now, these effects were considered strictly neuronal in nature. But because vascular endothelial cell motility is essential for heart development, the authors speculate that low levels of δ-catenin may also underlie the patients' cardiovascular abnormalities.

δ-catenin may be a promising anti-cancer target because eliminating or reducing its expression stunts only inflammation-induced vessel growth. First, however, the side effects on neuronal development must be investigated.



Vascular endothelial cells (green) express δ-catenin (red).

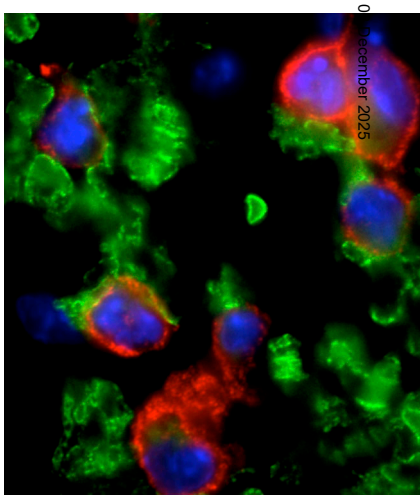
To dampen demyelination

T cells set off a multiple sclerosis–like disease in mice, but problems with a myeloid cell brake escalate the damage, according to a report by Xi and colleagues.

Various populations of immune cells invade the CNS during experimental autoimmune encephalomyelitis (EAE), a demyelinating disease in mice. One population—CD11c-expressing myeloid cells—provokes the destruction of myelin sheathes that protect nerves by presenting antigens to infiltrating T cells, and by producing inflammatory cytokines and reactive oxygen intermediates. Whether the latter secretions rely on the T cell response has remained elusive. Now, Xi et al. find that myeloid cells can wreak havoc without the help of T cells. And the destruction is heightened in the absence of a myeloid inhibitory receptor called CLM-1.

CLM-1 was expressed on CD11c-expressing myeloid cells that invaded the spinal cord during disease. Without CLM-1, demyelination and disease worsened rapidly—but not because the myeloid cells were more adept at activating disease-inducing T cells. In fact, the receptor inhibited CNS damage only after the disease began.

Whether multiple sclerosis patients bear defects in the human orthologue of CLM-1, CD300f, remains to be seen. If so, CLM-1 and its as-yet-unknown ligand could be manipulated to stifle inflammation in this and other demyelinating diseases.



The myeloid inhibitory receptor CLM-1 (red) prevents the release of damaging inflammatory cytokines during EAE.