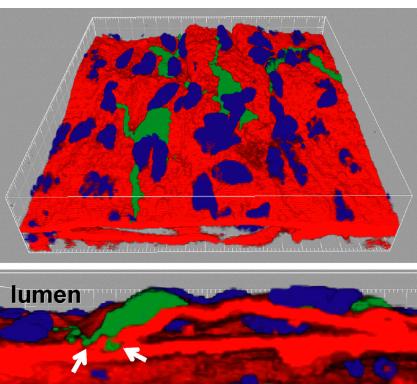
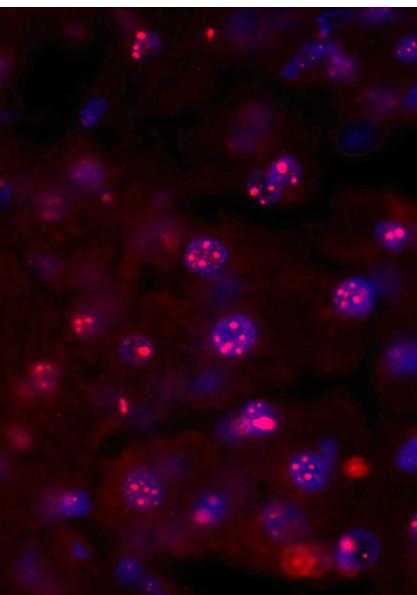


IN THIS ISSUE



Dendritic processes (arrows) are anchored in arterial tissue.



Autoantibodies are increased in DC-deficient mice.

New parts in beating hearts

Within turbulent regions of the heart, the spindly fingers of dendritic cells (DCs) probe pumping blood in search of antigens, Choi and colleagues demonstrate on page 497. Known for their role in both warding off and tolerating infection, these potent antigen presenters bring a new dimension to cardiovascular inflammation.

Choi et al. spotted DCs congregating at the base of the aorta and around cardiac valves in healthy, CD11c-EYFP transgenic mice. The cells nestled beneath the epithelium of the innermost vessel layers with some of their slim dendritic processes dangling into the lumen where they captured circulating molecules—much like DC processes in the intestines, lungs, and other organs do.

In independent studies with two model antigens (ovalbumin and a malaria protein), the authors showed that these cells not only looked like DCs but acted like them too. Aortic DCs cross-presented injected and blood-borne antigens to CD8⁺ T cells.

Compared with their contemporaries in the spleen, DCs of the aorta and heart valves expressed lower levels of costimulatory molecules, indicating that they may be resting in healthy mice. However, aortic cells expressing CD11c have been shown to increase during aging and atherosclerosis. Thus Choi et al. speculate that aortic DCs may lead to problems if triggered by insult or infection. Now that these researchers have determined that DCs are indeed there, they can begin to study their role in heart disease.

Dendritic cells teach tolerance

In a report that challenges existing ideas, Ohnmacht et al. find that depleting mice of their dendritic cells (DCs) leads to severe autoimmunity (page 549).

Earlier studies concluded that DCs weren't essential defenders against autoimmunity because mice were hardly affected by DC deletions. Although these cells help eliminate autoreactive lymphocytes in the thymus, B cells and other antigen-presenting cells (APCs) can do this too, suggesting that other APCs can compensate for the absence of DCs.

Here, Ohnmacht et al. find just the opposite. In mice born missing more than 90% of their DCs, over half died within the first few months of life from sudden and severe autoimmunity. Without DCs in the thymus, autoreactive T cells escaped into the periphery where they went unregulated. The authors also noted elevated levels of autoreactive CD4 T cells and autoantibodies within various inflamed tissues, which were presumably primed by the few remaining DCs and other types of APCs in the tissues. Th1 and Th17 cells, both known to contribute to autoimmune inflammation, were also elevated compared with controls.

Why previous studies reached different conclusions may be a matter of timing and technical detail. In some earlier experiments, DCs had been eliminated transiently during adult life, at which point most autoreactive T cells may already have been deleted in the thymus. And although the authors of the most recent study used a similar technique to eliminate DCs, they failed to get rid of all types of DCs, notably leaving Langerhans cells and plasmacytoid DCs behind.

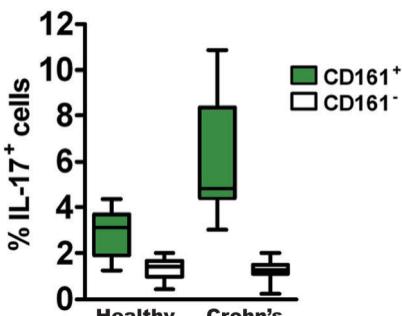
How DCs enforce self-tolerance in the periphery remains elusive. The quantity of regulatory T cells did not appear to change in the DC-deficient mice, indicating that changes in these inflammation suppressors were not behind the autoimmunity. However, peripheral DCs may be a source of IL-10 or TGF- β , proteins required to maintain self-tolerance.

Flagging Th17 in Crohn's

It doesn't take much to set off certain Th17 cells lurking in the intestines of patients with Crohn's disease. And on page 525, Kleinschek et al. find a marker that pinpoints those easy-to-incite cells.

Historically, T helper (Th)-1 cells were blamed for causing inflammation in Crohn's disease, psoriasis, and various autoimmune disorders. Interleukin (IL)-17-producing Th17 cells are also found in many of these diseases, although their role in disease pathology is poorly understood. To better characterize these newcomers, Kleinschek et al. examined tissue biopsies and blood samples from people with severe Crohn's disease.

In the inflamed intestinal tissue, the authors found an abundance of Th17 cells expressing the surface receptor CD161, which was recently shown to predict a Th17 fate for naive T cells in the thymus and umbilical cord. Here, the authors found that CD161 was present on differentiated cells that produced IL-17 and other Th17-type cytokines such as IL-17F and IL-22.



CD161⁺ T cells from patients with Crohn's disease preferentially express IL-17.

CD161⁺ T cells from the blood of Crohn's patients expressed more IL-17 and IL-23R, and could be quickly stimulated to produce inflammatory cytokines with IL-23 alone. Th17 cells from healthy participants required an additional cytokine, IL-1 β , for activation.

The abundant expression of gut homing integrins on circulating CD161⁺ Th17 cells suggests that these cells migrate to sites of intestinal inflammation.

Whether or not CD161 is mechanistically involved with the proliferation or differentiation of Th17 cells remains unknown. For now, the authors say that CD161 could provide a marker for clinicians to identify pathogenic T cells, thereby identifying patients who could be at risk of severe inflammatory bowel disorders.

TSPL calms inflammation

On the tumultuous shores of the intestinal epithelium, TSPL keeps the peace. When faced with a threat, the cytokine not only triggers a protective Th2 response, it also helps keep intestinal inflammation in check, suggest Taylor et al. on [page 655](#).

In the past few years, some researchers have classified TSPL as a “master regulator” of the Th2 response. However, that title may be premature, even though overexpression of the cytokine in pulmonary tissue and skin cells result in Th2-induced asthma and dermatitis. As Th2 responses also defend the body against worm infections, Taylor et al. turned to the gut to see if TSPL could be more than a harbinger of Th2-driven malady.

As predicted, mice could neither mount a Th2 response nor clear a worm infection when TSPL or its receptor were blocked. In fact, the intestinal inflammation in these mice was abnormally severe, most likely due to abundant expression of inflammatory cytokines such as IFN γ , IL-17, and IL-12/23p40.

The abundance of these cytokines meant that the ratio of CD4⁺ effector T cells was skewed away from Th2. And the aberrant expression of IFN γ , which suppresses Th2 cell differentiation, presumably maintains this imbalance. Indeed, neutralization of IFN γ rescued the Th2 response and restored anti-worm immunity in TSPL-deficient mice. TSPL might normally suppress Th1 responses by acting directly on dendritic cells (DCs), as treating activated DCs with TSPL hampered production of the Th1-promoting cytokine IL-12.

TSPL also proved important for ameliorating inflammation in a mouse model of colitis, suggesting a general anti-inflammatory role for TSPL in the gut.

By exposing TSPL's brighter side, the authors provide an explanation for why this protein may have been maintained during evolution. If TSPL did nothing more than fire up asthma-inducing Th2 cells, why would it still exist, reasons lead author David Artis. Perhaps it acquired the ability to both drive Th2 responses and control inflammation in the gut where these responses go hand-in-hand. TSPL seems to maintain a role in controlling inflammation in humans as well. In a recent survey of Crohn's disease patients, intestinal inflammation was worse in those with less TSPL.

A syndecan-based tumor stopper

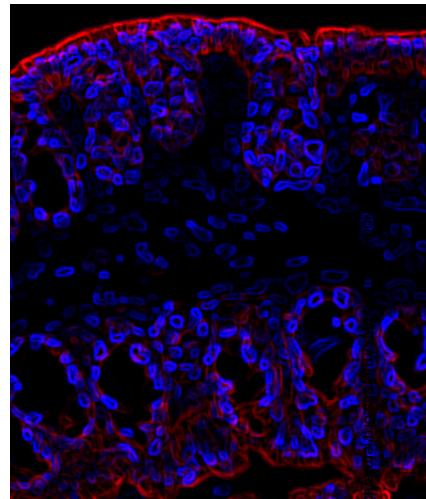
Successful tumors supply themselves with a steady source of blood by triggering the growth of new vessels. On [page 691](#), Beauvais et al. find a new way to disrupt that process.

Metastatic tumors up-regulate the integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$, which prompt endothelial cells to multiply, migrate, and thus lay down new vessel branches. Integrin activation requires a connection between the integrin and the cell matrix, which is provided by the matrix receptor syndecan-1. In past studies, these authors showed that syndecan-1 was necessary for integrin activation in breast cancer cells *in vitro*.

Pharmacological integrin inhibitors have recently been developed and are being tested for their efficacy as tumor-stopping agents. But blocking syndecan-1 may be even more effective, suggest Beauvais et al. Here, the authors blocked the integrin–syndecan–matrix interaction with a peptide (“synstatin”) derived from syndecan's site of integrin engagement.

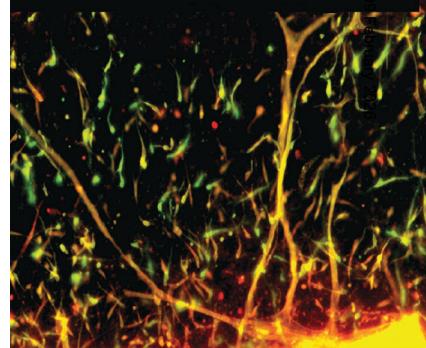
When synstatin is present, syndecan–integrin clusters cannot form, and integrin activation is blunted. Synstatin blocked integrin activation on vascular endothelial cells *in vitro*, the authors found. And injecting synstatin into mice slowed tumor growth and new vessel formation. Synstatin also impeded vessel growth in a mouse model of corneal angiogenesis.

By preventing integrins from engaging the matrix, the authors expect a more thorough block of integrin signaling than can be achieved with other kinds of inhibitors. Although some pharmacological peptides are rapidly cleared from circulation before they can act, synstatin's long-lasting effects in mice suggests that this may not be a problem.



Intestinal TSPL (red) protects against chronic worm infection.

Syndecan/integrin



The coexpression (yellow) of syndecan-1 and integrins in tumors drives angiogenesis.