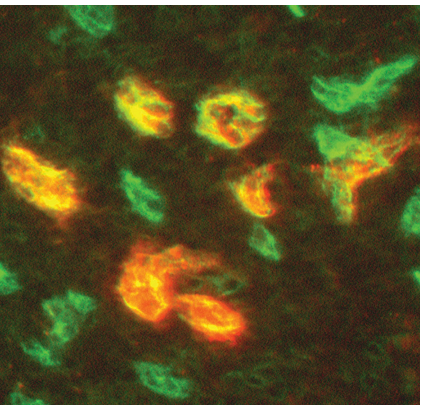


Imiquimod induces the expression of E-selectin (yellow) on blood vessels in skin tumors.

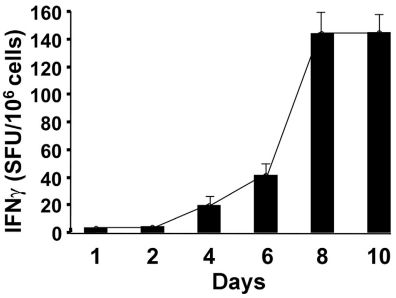
Tumor-fighting T cells lose their way

Like a tourist without a map, tumor-fighting T cells have a hard time finding their destination without directions. According to Clark et al. (page 2221), dismantling these directions helps skin cancer cells hide from killer T cells.

To enter the skin, T cells must grab on to the adhesive molecule E-selectin, which is expressed on the endothelial cells lining blood vessels in the skin. The authors now find that many of the vessels in skin cancer lesions lack E-selectin, causing beneficial T cells to pass by unaware. The tumors were instead populated by suppressive regulatory (T reg) cells, perhaps coaxed in by the tumor to safeguard against killer cells that somehow gain access. Both tactics have also been seen in other types of human cancer.

Reversing the suppressive effect of T reg cells is one of the beneficial effects of topical immune-stimulating drugs like the TLR agonist imiquimod, which is effective in treating certain types of skin cancer. Indeed, Clark et al. found that imiquimod treatment reduced both the percentages and function of tumor-infiltrating T reg cells. To the authors' surprise, the drug also induced E-selectin expression on tumor vessels, restoring T cell road signs and allowing killer T cells to invade the tumor.

How tumor cells turn off E-selectin and how imiquimod turns it back on are not yet known, but both effects required neighboring antigen-presenting cells (APCs) in the tumor. After imiquimod treatment, most APCs were mature dendritic cells—the most potent T cell stimulators. The effects of topical imiquimod on T reg cells are temporary, but may last just long enough to allow killer T cells to destroy the tumor without throwing off the normal balance of T cells in the skin. **RB**



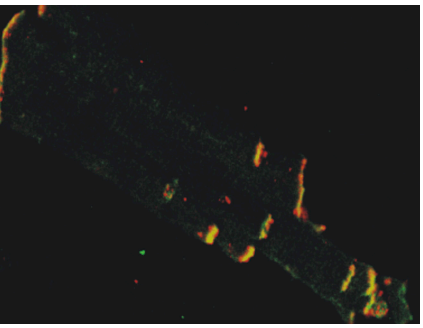
Delayed development of interferon-γ–producing Th1 cells in newborns.

Tardy DCs to the (Th1) rescue

In newborns, the sluggish appearance of one cell population means death to another, according to Lee et al. on page 2269. These results may help explain why newborns are highly susceptible to certain infections.

Newborn mice exposed to antigen respond by activating both T helper (Th)-1 and Th2 cells. Yet a second exposure causes allergy-promoting Th2 cells to thrive but microbe-fighting Th1 cells to die. Previous work by this group showed that antigen exposure during the first few days of life caused Th1 cells to express the cytokine receptor chain IL-13Rα1, a receptor not commonly found on these cells, which then teamed up with the IL-4Rα chain. The resulting heteroreceptor induced Th1 cell death when triggered by Th2-promoting IL-4 during secondary antigen exposure.

At six days of age, the authors now show, Th1 cells had a reversal of fortune. The turning point was marked by the appearance of a subset of antigen-presenting CD8α+ dendritic cells (DCs) that churned out life-saving IL-12. Giving newborns extra IL-12, which is feebly produced before day 6, or providing them with IL-12–producing DCs blunted the expression of IL-13Rα1 and rescued the Th1 cells. What delays the development of this DC population relative to other subsets remains unknown. **RB**



The loss of CAR (green) expression leads to cardiac arrhythmia because connexins (red) are no longer held in place at heart AV nodes.

CAR keeps up the (heart) beat

A cell contact protein found in the heart does more than provide structural support, according to Lisewski et al. (page 2369). It also helps maintain a steady heartbeat.

In developing or injured heart muscle, a cell–cell adhesion protein known as the Coxsackievirus–adenovirus receptor (CAR) helps growing muscle fibers stick to each other and settle into place. The relatively low levels of CAR in adult hearts suggest that they've outgrown the need for it. But the authors now find that this bit of CAR keeps ion channels called connexins in place, thus aiding the transmission of electrical connections between heart cells.

Decreasing CAR expression in the heart, the group found, did not disrupt the structural stability of the organ but triggered an erratic heartbeat. Electrical signals within each heart chamber were normal, but they were delayed in passing from atria to ventricles.

Electrical signals pass between the chambers through a cell cluster called the atrial-ventricular (AV) node, via ion channels made of connexins 45. The AV node cells of CAR-deficient mice had fewer of these connexins, which drifted throughout the cell membrane instead of clustering

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at gap junctions, where they belong. Although it's possible that CAR-driven signals induce connexin gene expression, the recent discovery that the two proteins bind to each other suggests instead that CAR might pin down connexins in adjacent gap junctions, thereby preventing their mislocalization and subsequent degradation.

The findings might explain the association between cardiac arrhythmia and CAR loss seen in patients who develop autoantibodies against CAR or who become infected with Coxsackievirus. The group is now trying to confirm that this arrhythmia is due to a connexin disturbance at the AV node. **HB**

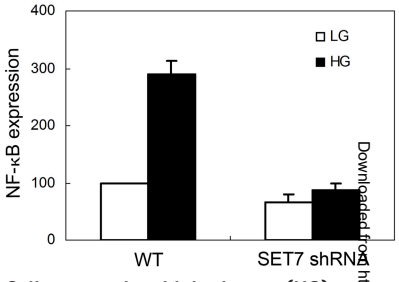
The lowdown on sugar highs

Short-lived sugar highs might give a quick energy boost, but according to El-Osta et al. (page 2409), they also leave a lasting bad impression on heart vessels of diabetes patients. The findings might explain why diabetics are at higher risk for heart disease.

Diabetes is a major cause of heart attack and stroke—events that are triggered by atherosclerotic plaques and inflammation in the arteries. In diabetic patients who have had extended periods of high blood glucose levels, arterial damage persists long after insulin therapy reduces their mean glucose levels. The authors now provide a molecular explanation for this phenomenon.

The group found that short-lived sugar highs, which occur even in insulin-treated diabetics, trigger histone modifications—an established effect of long-lasting sugar highs. Persistently high sugar levels are known to create reactive oxygen species that induce the generation of methylglyoxal—an activator of the histone methylating enzyme Set7. The authors found that brief blood sugar peaks also activated Set7, which bound to the promoter of the gene for NF-κB, thereby increasing its expression. NF-κB then switched on genes for proteins that help recruit and attach plaque-forming monocytes to vessel walls. These gene expression changes, which were seen in both human heart endothelial cells and mouse aortas, persisted for at least six days after glucose levels returned to normal. These changes were prevented by blocking methylglyoxal production.

Current treatments for diabetes are aimed at reducing mean glucose levels in patients but not the temporary rises in blood sugar levels that occur between insulin injections. This study suggests that adjusting the timing of the treatment regimen to avoid these spikes might be more effective in reducing the risk of heart disease. **HB**



Cells exposed to high glucose (HG) levels overexpress NF-κB due to histone modifications of the NF-κB promoter by the enzyme Set7.

Egr-2 prevents self-reactions

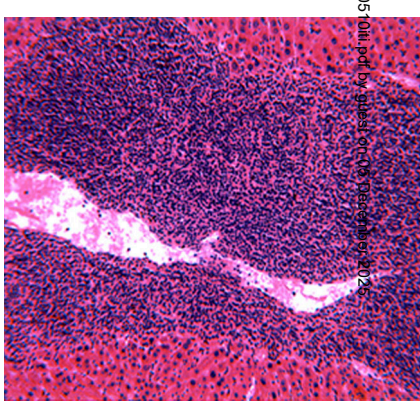
Self-tolerance is well known to be enforced in part by an external force of regulatory T cells. Now, Zhu et al. (page 2295) show that T cells also have their own internal barrier to self-reactivity—a transcription factor called Egr-2.

The team had previously found that Egr-2 is made by T cells that are repeatedly stimulated by their cognate antigen. The cells then become unresponsive, much like T cells that are constantly exposed to self-antigens in the periphery.

The authors now find that, in mice, Egr-2 expression is also turned on in effector T cells that develop as a result of exposure to gut bacteria or to certain self-antigens. The Egr-2–expressing cells reacted to strong T cell receptor stimulation in vitro but did not trigger autoimmunity or responses against the gut bacteria in mice, suggesting that Egr-2 might only temper T cell reaction to the relatively weak signals of self-antigens. But how repeated antigen stimulation induces Egr-2 and how the transcription factor distinguishes weak, self-signals from strong, non-self signals are not yet known.

The deletion of Egr-2 triggered the accumulation of effector T cells and the development of lupus and its accompanying inflammation. The T cells amassed due to reduced expression of the gene for the cell cycle inhibitor p21Cip1, one of the few known Egr-2 targets. The rapidly proliferating T cells overexpressed genes for inflammatory cytokines, but the authors have yet to determine which Egr-2–induced genes normally suppress these cytokine genes.

Persistent viral antigens are known to induce tolerance in effector T cells, resulting in chronic infections. The group is now investigating whether deletion of Egr-2 in these cells prevents chronic infection. **HB**



Overproliferating T cells infiltrate the liver and trigger lupus-like autoimmunity in older Egr-2–deficient mice.