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.

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.

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 43. The AV node cells of CAR-deficient mice had fewer of these connexins, which drifted throughout the cell membrane instead of clustering...