Paving the way to metastasis

Tumors must invade lymph nodes to become metastatic, but how the tumor cells make this trip is not completely clear. On page 1089, Hirakawa and colleagues show that a tumor-derived growth factor stimulates the formation of new lymphatic vessels in the nearby lymph node, even before any tumor cells arrive. This suggests that the tumor may instruct the lymph node to prepare for its arrival.

Stimulation of lymphatic growth has for some time played second fiddle to angiogenesis. During angiogenesis, tumors produce factors such as vascular endothelial growth factor-A (VEGF-A) that induce vessel growth and thus greater nutrient supply. Recently, however, two relatives of VEGF-A, VEGF-C and VEGF-D, have been shown to induce lymphangiogenesis within tumors. Although earlier studies suggested that VEGF-A could also induce lymphangiogenesis, this had never been shown in a tumor model and remained controversial.

Hirakawa et al. now show that expression of VEGF-A by skin cells causes mice to develop cancer more rapidly in response to a chemical carcinogen. Both blood vessel and lymphatic vessel growth were increased in VEGF-A-expressing skin tumors, a result that was consistent with their earlier observations that VEGF-A could induce the proliferation of lymphatic endothelial cells in culture.

VEGF-A induced active lymphatic proliferation both within the tumor and in the nearby lymph node, possibly explaining the increased metastasis of VEGF-A-expressing tumors. Lymphatic growth in the lymph node began—to the authors’ surprise—before tumor cells arrived on the scene, suggesting that VEGF-A expression may help initiate tumor metastasis.

The angiogenic activity of VEGF-A was previously thought to be restricted to the immediate tumor vicinity. The authors now suggest that VEGF-A is drained from the tumor through both preexisting lymphatic vessels and the lymphatic vessels it helped construct. They are now investigating relative timing to see if tumor-localized lymphangiogenesis might be a prerequisite for node-localized lymphangiogenesis. JEM

Killer combinations for cervical cancer

Certain combinations of HLA class I genes and natural killer (NK) cell receptors increase the risk of developing cervical cancer, according to a study by Carrington and colleagues on page 1069. Women who possess HLA alleles that engage inhibitory NK cell receptors were less likely to develop cervical cancer, suggesting that NK cell activation may promote cancer development.

Most cervical cancers (>95%) are associated with human papillomavirus (HPV), which establishes chronic infections in the genital tract. HPV infections that do not result in cancer may be due to effective cellular immune responses that limit HPV replication. NK cells are found in HPV-positive cervical lesions and may help protect against the virus. NK cell activation hinges on a balance between activating and inhibitory signals generated in part by a diverse group of NK cell receptors—killer cell immunoglobulin-like receptors (KIRs)—that bind HLA class I molecules on interacting cells. Combinations of KIR and HLA genes that promote either NK cell activation or inhibition have been associated with increased susceptibility to various viral and autoimmune diseases.

Carrington and colleagues found that individuals whose HLA molecules primarily bound to inhibitory KIRs had a decreased risk for cervical cancer, those with certain activating HLA–KIR combinations had increased risk. NK cell activation may contribute to local inflammation, suggests Carrington, which has been associated with the progression of other types of cancer, including gastric and prostate cancer. But how NK cell activation might promote transformation remains unknown. JEM
Controlling unruly osteoclasts

Monocytes beget macrophages, and fused macrophages beget bone-resorbing osteoclasts. Factors such as monocyte-colony stimulating factor (from stromal cells) and interleukin-1 (IL-1; from macrophages) keep this process ticking along, but now Li et al. examined the function of this process in osteoclasts. They found that mice lacking IRAK-M had increased numbers of osteoclasts, which lived longer and were more responsive in bone-resorbing osteoclasts. Genetic mutations that cause aberrant activation of the RANKL signaling pathway have been identified in some cases of severe, inherited osteoporosis—the authors think IRAK-M mutations might be to blame for other unexplained cases. JEM

Overstimulated and ineffective

CD4+ T cells become ineffective if repeatedly stimulated through their T cell receptors (TCRs), according to a study by Jelley-Gibbs and colleagues on page 1101. The functional demise of these cells may help explain why persisting pathogens, such as Mycobacterium tuberculosis and HIV, are associated with ineffective CD4+ T cell responses during the chronic phase of infection.

Chronic infections have been shown to induce exhaustion or functional unresponsiveness in cytotoxic CD8+ T cells, but their effect on CD4+ T helper cells has not been well studied. Jelley-Gibbs et al. now show that repeated stimulation of CD4+ T cells generated effector cells that were more activated, based on the expression of activation markers CD69 and CD62L, than cells stimulated only once but that secreted lower levels of the cytokines interferon-γ (IFN-γ) and interleukin-4 (IL-4). These repeatedly stimulated cells could not provide help to antibody-producing B cells, nor could they protect against influenza virus infection when transferred into mice.

The decreased function of these repeatedly stimulated cells could not be explained by the down-regulation of their TCRs, whose levels were only marginally affected by the multiple rounds of stimulation. The authors are now studying chromatin remodeling at the IFNγ and IL-4 loci for possible clues to the decreased cytokine production. JEM

The way to the skin

Memory CD4+ T cells express characteristic adhesion molecules and chemokine receptors that dictate their recirculation to the tissue in which they first encountered antigen. On page 1045, Baekkevold and colleagues show that T cells may compete for access to the skin and only gain entry if they express the CC-chemokine receptor-4 (CCR4).

Previous studies showed that skin-homing and gut-homing CD4+ T cells express distinct chemokine receptors—CCR4 for skin-homing cells and CCR9 for gut-homing cells—and this was mirrored by the expression of the corresponding chemokine ligand in local blood vessels. The authors thus proposed that expression of CCR4 was required for T cells to access the skin (and CCR9 for the gut) but were perplexed by the phenotype of CCR4-deficient mice, which had normal numbers of skin-homing T cells.

Another skin-specific chemokine receptor may have compensated for the absence of CCR4. To test this, Baekkevold et al. staged a competition between wild type and CCR4-deficient bone marrow cells in lymphocyte-deficient mice. They found that CCR4+ cells were highly enriched among lymphocytes that trafficked to the skin, particularly during skin inflammation. This suggested that CCR4, although not essential, facilitated the generation of the skin-homing memory T cell population.

Recent studies have shown that tissue-specific dendritic cells (DC) impart CD8+ T cells with specific homing instructions and the authors suspect that a DC-derived signal may trigger CCR4 expression and similarly instruct CD4+ T cells. JEM