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In This Issue

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IL-7 sweeps HIV-1 hideouts The persistence of HIV-1 in virally suppressed infected individuals on highly active antiretroviral therapy (HAART) remains a major therapeutic problem. Additional immune activation therapy utilizing IL-2 has shown some potential to stimulate latent proviruses in these individuals. Roger Pomerantz, Giuseppe Nunnari, and colleagues now demonstrate that IL-7 is a unique and potent inducer of HIV-1 proviral activation from both resting CD4+ T lymphocytes and PBMCs from virally suppressed HIV-1–infected individuals on HAART (pages 128–137). Their phylogenetic analyses of viral envelope gp120 genes from induced viruses indicate that a distinct proviral quasispecies had been activated by IL-7. During relatively long-term treatment, low levels of activation parameters and cell cycling do occur, contrary to what has been shown in other studies. IL-7, while performing its immunomodulatory function, may simultaneously stimulate HIV-1 replication from resting CD4+ T lymphocytes to deplete HIV-1 reservoirs. These data demonstrate that different activators of proviral latency may perturb and potentially deplete only selected, specific portions of the proviral archive in virally suppressed individuals. The immunomodulatory effects of IL-7 could potentially be combined with its ability to stimulate HIV-1 replication to deplete HIV-1 reservoirs.PDGF-CC: the best thing since sliced bread? The traditional PDGF family members (PDGF-AA and -BB) have been demonstrated to play critical roles in embryonic development, mesenchymal cell proliferation, and migration. In sharp […]

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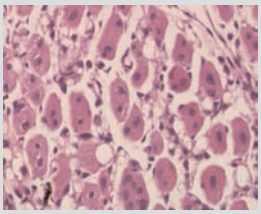
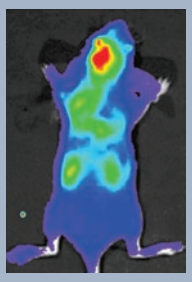


PDGF-CC: the best thing since sliced bread?

The traditional PDGF family members (PDGF-AA and -BB) have been demonstrated to play critical roles in embryonic development, mesenchymal cell proliferation, and migration. In sharp contrast, the in vivo functions of the newly discovered PDGF-CC are, to date, still largely unknown. Peter Carmeliet and colleagues now further characterize the in vivo biological activities and explore the cellular and molecular mechanisms and therapeutic potential of PDGF-CC (pages 118–127). The authors show that PDGF-CC stimulates functional vessel growth and perfusion in the ischemic heart and limb and improves tissue regeneration in vivo. Carmeliet and colleagues show that PDGF-CC stimulates angiogenesis and also speeds the new vessels' maturation and stabilization via recruitment of smooth muscle cells. PDGF-CC mobilized endothelial progenitor cells, induced differentiation of bone marrow cells into endothelial cells, stimulated migration of endothelial cells, and upregulated VEGF expression. PDGF-CC offers novel therapeutic opportunities, especially when one considers that few molecules with a similar pleiotropic activity profile have thus far been identified.



Breast cancer's signature style

Cancer metastases, which are responsible for the majority of cancer-related deaths, probably arise from rare cells in the primary tumor that acquire the ability to progress through the sequential steps necessary to grow at a distant site. DNA microarray technology, which allows for genome-wide transcriptomic profiling, has provided new insight into the genetic basis of metastasis. Now Joan Massagué and colleagues use this technology to uncover the genetic signature of metastatic cells (pages 44–55). The authors used a combination of noninvasive bioluminescence imaging and fluorescence histology to demonstrate distinct patterns of organ-specific metastatic behavior by individual cells from a population of human breast cancer cells established in culture from a malignant pleural effusion. The single cell–derived populations had varying abilities to colonize and grow in bone, lung, and adrenal medulla. The different metastatic behaviors did not correlate with the "poor-prognosis" gene expression signature, as all of the single cell–derived populations similarly expressed this signature. In contrast, unsupervised classification methods using the transcriptomic dataset showed that metastatic tropism is governed by metastasis-specific genes separate from the poor-prognosis signature. Furthermore, a gene expression signature for bone metastasis was able to distinguish primary breast carcinomas that preferentially metastasized to bone. Understanding bone-specific metastatic phenotypes and a gene expression signature may help guide treatment of breast cancers.

Intestinal macrophages eat without getting upset

Intestinal macrophages, which are derived from blood monocytes, are thought to orchestrate mucosal inflammatory responses. However, Lesley Smythies and colleagues now show that resident intestinal macrophages lack many innate response receptors and do not produce proinflammatory cytokines such as IL-1, IL-6, IL-8, and TNF-α, although the cells retain phagocytic and bacteriocidal activity (pages 66–75). To illustrate how noninflammatory intestinal macrophages are distinct in phenotype and function from their proinflammatory precursors, the authors show that intestinal stromal cell–derived products downregulate monocyte receptor expression. Stromal cell–derived products also downregulated cytokine production, but not phagocytic or bactericidal activity. The downregulation of innate response receptors and surface antigens was found to be regulated by factors derived from stromal cells, but not epithelial or lamina propria mononuclear cells. These findings indicate a mechanism by which highly proinflammatory monocytes recruited to the intestinal mucosa acquire profound inflammatory anergy but retain scavenger and host defense function.