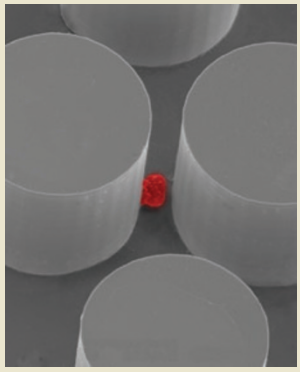
Posthaste tumor cell detection



Oncologists have long appreciated the diagnostic potential of circulating tumor cells (CTCs). Nonetheless, the fragility and scarcity of CTCs in blood samples from patients with even aggressive metastatic cancer have thwarted their isolation, enumeration and analysis. Now, Toner and colleagues describe a microfluidic device comprising 78,000 antibody-coated microposts over 970 mm^3, which traps CTCs expressing anti-epithelial cell-adhesion molecule (EpCAM) when ~3 ml of unprocessed whole blood is passed through it under specific flow conditions. The chip recovered CTCs from 115 of 116 blood samples from 68 patients with metastatic lung, prostate, pancreatic, breast or colon cancer. Enrichment of viable CTCs from nonspecifically bound blood cells was ~100-fold better than with alternative technologies. The device should facilitate both better understanding of metastasis and faster, noninvasive monitoring and guidance of cancer therapies. (*Nature* **450**, 1235–1239, 2007) *PH*

Heartbeat from a ghost

Removing the cells of an organ while preserving its tissue matrix creates a biological scaffold that can be reseeded with fresh cells to study organ development and regeneration. Taylor and colleagues have applied this approach to the adult rat heart, producing constructs with weak left ventricular pressure and contractile function. First, cadaveric hearts were decellularized by perfusing them with detergent. The hearts were then reseeded with neonatal cardiac cells by intramural injection and cultured for up to 4 weeks in bioreactors that provided coronary perfusion and oxygenated media. Electrical stimulation was delivered through epicardial leads. Histological analysis of the resulting structures showed recellularization near the injection sites, expression of cardiac markers and the presence of immature cross-striated contractile fibers. Functional tests revealed that the hearts had acquired a pumping force equal to ~2% of that of the adult rat heart. (*Nat. Med.*, published online 13 January 2008; doi:10.1038/nm1684) *KA*

HIV's henchmen revealed

With only 15 encoded proteins, HIV-1 relies primarily on host cell functions for its propagation. Inspired by the prospects that drugs targeting this hitherto poorly characterized subset of human proteins might block HIV infection or replication, Elledge and colleagues describe a genome-wide RNA interference screen that reveals 273 HIV-dependency factors. Of these, only 36 were previously implicated in HIV pathogenesis. The authors evaluate viral progression in >21,000 pools of human cells—effectively representing knockouts of all human genes—by assessing the infectious capacity of the cells and scoring for the presence of the viral Gag protein. Functional clustering and validation implicates autophagy, retrograde trafficking of vesicles from endosomes to the Golgi, and special roles of a karyopherin and the Mediator complex in the HIV life cycle. As human proteins are not under the same selective pressure as viruses to mutate, host targets may not develop drug resistance as rapidly as their viral counterparts. (*Sciencexpress*, published online 10 January 2008; doi: 10.1126/science.1152725) *PH*

MicroRNAs and breast cancer

Two papers outline a key role for microRNAs (miRNAs) in breast cancer progression. Song, Lieberman and colleagues present results in *Cell* showing that *let-7* miRNAs regulate the self-renewal and tumorigenicity of breast cancer cells: *let-7* expression is reduced in breast tumor-initiating cells, but increased in differentiated cells. Lentiviral transduction of *let-7* into breast tumor-initiating cells reduced their proliferation and ability to remain undifferentiated *ex vivo*, as well as suppressing tumor formation and metastasis in mice. Conversely, antisense inhibition of *let-7* in nontumor-initiating cells enhances *ex vivo* self renewal. The authors argue that *let-7* is a master regulator of stem cell properties because increased *let-7* expression in tumor-initiating cells reduces expression of the known *let-7* targets H-RAS and HMGA2. In another paper, Massagué and colleagues identify three miRNAs that suppress metastasis in human breast cancer. Whereas retroviral transduction of malignant breast cancer cells with miR-126 reduced tumor growth and proliferation, ectopic expression of miR-206 or miR-335 inhibited metastatic cell invasion. The miR-335 regulates metastasis by inhibiting expression of the transcription factor SOX4 and the extracellular matrix component tenascin C. Future experiments are required to determine whether modulation of *let-7*, miR-335 or miR-206 expression in breast cancer can be used therapeutically. (*Cell* **131**, 1109–1123, 2007; *Nature* **451**, 147–152, 2008) *JWT*

Reorienting mesenchymal stem cells

Mesenchymal stem cells (MSCs) could provide therapy for untreatable skeletal diseases, like osteoporosis and osteogenesis imperfecta, but for their inability to home to the bone marrow. Now, Sakstein *et al.* have shown that enzymatic treatment of the MSC surface glycoproteins enables them to get to the bone marrow and initiate bone production in mice. The route to the bone marrow requires binding between a homing receptor, E-selectin, on the microvasculature and surface glycoproteins (P-selectin ligand 1 and an α-1,3-sialofucosylated CD44) present on hematopoietic progenitor cells. Whereas MSCs do not display those receptors, they do have an α-2,3-sialofucosylated CD44. The authors thus tried modifying the terminal sugar to see if that would change MSC tropism *in vivo*, and showed that the engineered MSCs reacted with antibodies directed against a1,3-sialofucosylated glycoproteins, bound to human endothelial cells in a flow chamber, and homed to bone marrow in immunocompromised mice. What's more, islands of human $CD44^+$ cells with osteocalcin deposits were found within the bones of injected mice, suggesting that modified MSCs can differentiate *in vivo*. Beyond its clinical implications, the methodology could prove useful for studying conditions, such as inflammation and cancer, that involve selectin expression. (*Nat. Med.*, published online 13 January 2008; doi:10.1038/nm1703) *LD*

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