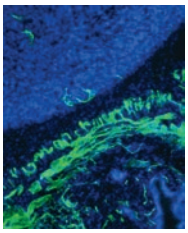
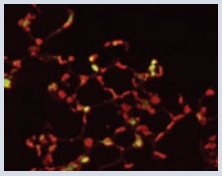
Tumors walk; semaphorins block



Melanoma is the deadliest form of skin cancer, primarily because of its highly metastatic nature. One class of proteins called semaphorins could play a role in the development of tumor metastasis as they have been shown to inhibit the migration of neuronal and endothelial cells. Michael Klagsbrun and colleagues examined semaphorin 3F (SEMA3F) expression in human metastatic cancer cell lines and found that it was markedly lower both in cell culture and in implanted tumors in mice (pages 1260–1271). The authors transfected SEMA3F into human melanoma cells. In culture, these cells had reduced ability to adhere to and migrate on fibronectin. They were also chemorepulsive for vascular and lymphatic endothelial cells that expressed neuropilin-2 in a manner consistent with semaphorin-mediated chemorepulsion of neurons. This chemorepulsive activity was blocked with neuropilin-2 small inhibitory RNA treatment. For in vivo analysis, the authors implanted these transfected tumor cells in mice. In drastic contrast to the mock-transfected tumors, the SEMA3F-transfected tumors did not metastasize. Furthermore, the resultant primary tumors resembled benign nevi that had increased apoptotic cell numbers and reduced vascularization. Hyperplasia was inhibited in overlying epidermal cells, and the tumors were encapsulated in well-defined thick layers of fibroblast and collagen matrix. Together, these data indicate that SEMA3F is a strong inhibitor of metastasis that affects both tumor and stromal cells, which suggests that it may have therapeutic potential.

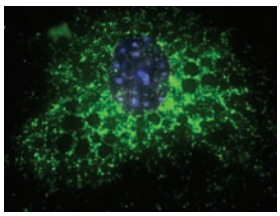
Breathe easier by reducing oxidative stress



Pulmonary emphysema is a major manifestation of chronic obstructive pulmonary disease, which affects more than 16 million Americans and is the fourth highest cause of death in the United States. This disease is primarily cigarette smoke induced (CS induced), but oxidative stress has recently been alleged to play an important role in pulmonary susceptibility to CS-induced damage. To investigate the impact of oxidative stress on emphysema development, Shyam Biswal and colleagues disrupted in mice the nuclear factor, erythroid-derived 2, like 2 (*Nrf2*) gene— a transcription factor involved in detoxification and antioxidant gene regulation (pages 1248–1259). Using computer-assisted morphometry, the authors found that CS-induced emphysema was of earlier onset and more widespread in the $Nrf2^{-/-}$ mice than in their wild-type littermates. The $Nrf2^{-/-}$ mice also had a greater number of apoptotic alveolar septal cells, prominent bronchoalveolar inflammation, and increased expression of the oxidative stress marker gene 8-oxo-7,8-dihydro-2′-deoxyguanosine. Microarray analysis provided evidence of about 50 Nrf2-dependent antioxidant and cytoprotective pulmonary genes that might function together to protect the lung from CS-induced emphysema. These data suggest that the Nrf2 pathway provides protection from emphysema by upregulating antioxidants and suppressing inflammation and apoptosis in the lung.

Energizing fat

Energy homeostasis is controlled by a complex series of cellular and endocrine interactions. White adipose tissue has been shown by mouse-knockout studies and the identification of adipose-specific secreted factors to be central to this process. Therapeutics for type 2 diabetes that enhance sensitivity to insulin, such as rosiglitazone, work through adipose tissue. In vitro work has indicated that rosiglitazone alters mitochondrial morphological features and protein profiles. Silvia Corvera and colleagues examined the in vivo effects of rosiglitazone through studies on white adipose tissue in *ob/ob* mice (pages 1281–1289). The authors found that at the onset of obesity in the *ob/ob* mice, there was decreased expression for about 50% of the mitochondrial protein genes. When these mice were treated with rosiglitazone, half of these genes showed upregulated expression. Additionally, the mitochondria in the white adipocytes of treated *ob/ob* mice had increased mass and altered structure. The oxygen consumption and oxidation of palmitate by these adipocytes were also significantly higher. The work here provides in vivo evidence that rosiglitazone treatment works by modifying mitochondrial structure and increasing white adipose tissue energy, which indicates that increased lipid utilization by adipocytes improves insulin sensitivity and alters whole-body energy homeostasis.



Imatinib able to inhibit c-Abl–induced fibrosis

Idiopathic pulmonary fibrosis (IPF) is a rapidly progressing lung disease that has a survival rate of fewer than three years. Recent work suggests an underlying mechanism of pathogenesis of IPF may work through profibrotic cytokines, such as TGF-β and PDGF, that promote fibroblast dysregulation. The proto-oncogene c-Abl is a downstream target of PDGFR. Edward Leof and colleagues examined TGF-β–induced fibrosis to determine if it is also mediated via c-Abl action (pages 1308–1316). The authors show that c-Abl is a direct target of TGF-β and that its kinase activity is stimulated by TGF-β in a Smad2/3-independent manner. Further, TGF-β stimulation of c-Abl kinase activity did not require PDGFR phosphorylation or expression. Use of imatinib, an FDA-approved treatment for chronic myelogenous leukemia that inhibits c-Abl family kinases, blocked TGF-β–induced fibroblast morphological changes and proliferation in culture. In vivo, imatinib treatment in a bleomycin-induced pulmonary fibrosis mouse model resulted in reduced collagen deposition and tissue destruction in addition to a lower number of inflammatory cells in lung tissue compared with that found in untreated mice. This study provides evidence that c-Abl family members may be primary targets of profibrotic cytokine signaling and that imatinib represents a potentially effective in vivo therapy for growth-dependent fibrosis in an animal model.