New Target to Treat Lung Disease

Idiopathic pulmonary fibrosis (IPF) often results in irreversible lung damage and respiratory failure. As the coagulation cascade has been implicated in IPF, Borenstajn et al (Am J Pathol 2010, 177:2753–2764) hypothesized that protease-activated receptor-2 (PAR-2), which is activated by the coagulation cascade, was involved in IPF pathogenesis. PAR-2 was up-regulated in patients with IPF as well as in a mouse model of IPF. Mice deficient in PAR-2 had less severe fibrosis, with fewer myofibroblasts and reduced levels of collagen deposition. These data implicate PAR-2 as a novel target for treatment of IPF.

Matrix-Metalloproteinase 9 (MMP-9) Involved in Cell Division

MMP degradation of the extracellular matrix is required for cancer metastasis and wound healing; however, the intracellular function of these molecules remains to be defined. Sans-Fons et al (Am J Pathol 2010, 177:2870–2885) found higher levels of MMP-9 activity in neuroblastoma cells and bone marrow macrophages undergoing mitosis compared with resting cells. They then compared MMP-9 expression with microtubule location; these data suggested MMP-9 participation in both nuclear reorganization and chromatid segmentation. Indeed, MMP inhibitors impaired cell cycling and reduced cell culture growth. These data indicate that MMP-9 may play an intracellular role in cell division and cycling in neuroblastoma and macrophage cells.

Parasites Block the Immune Response

The intracellular parasite Leishmania infects the phagocytic cells of the immune system. One type of phagocytic cell, the dendritic cell, is an antigen-presenting cell critical for priming and polarizing T cells to fight infection. Neves et al (Am J Pathol 2010, 177:2898–2911) explored the effects of Leishmania infection on dendritic cell maturation and activation. They found that infection did not induce dendritic cell maturation and also prevented maturation due to other stimuli. This inhibition was mediated by the PI3K/Akt and ERK1/2, but not the JNK and p38/MAPK, signaling pathways. In addition, parasitic infection resulted in cleavage of the proinflammatory molecule NF-κB. Thus, Leishmania promotes immune evasion by co-opting host signaling pathways.

Leptin Links Obesity and Tumor Growth

Obesity increases a patient’s risk of developing many types of cancer, including breast cancer. Leptin, which regulates food intake and energy homeostasis, has been suggested to play a role in mammary tumorigenesis; however, the mechanism governing these effects remains unclear. Using a mouse model deficient in the peripheral leptin receptor, Park et al (Am J Pathol 2010, 177:3133–3144) report attenuated tumor progression and metastasis. This effect was dependent on Jak2/STAT3 pathways and was tumor-cell autonomous. Mitochondrial function was preserved in these cells, which had an enhanced capacity for β-oxidation. Taken together, these results suggest that local leptin levels may play a major role in tumor progression in the mammary gland.

Nonspecific Tumor Inhibition by Small Interfering RNAs (siRNAs)

Hepatocellular carcinoma, which is the third largest cause of cancer-related deaths, has limited treatment options. Gene silencing techniques have been suggested for both treating established hepatocellular carcinoma and preventing cancer development by treating underlying disease. Bergé et al (Am J Pathol 2010, 177:3192–3201) examined the effects of both nonspecific control and neuropilin-1–specific siRNA in an animal model of hepatocellular carcinoma. Both control and specific siRNAs resulted in decreased tumor volume and vascular remodeling. Moreover, Toll-like receptor 3 (TLR-3) was up-regulated in hepatocellular carcinoma, and polyinosinic-polycytidylic acid (a TLR-3 agonist) mediated similar tumor regression and antiangiogenic effects. Both TLR-3 and siRNA treatment inhibited endothelial cell proliferation in an interferon-γ–specific manner. Therefore, siRNA may inhibit tumor angiogenesis nonspecifically by blocking endothelial cell proliferation.