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This Month in *AJP*

Seeing Deeper Leads to Deeper Understanding

The early detection of internal organ disease is critical to accurate diagnosis, management, or cure. Magnetic resonance (MR) imaging has aided the transformation of diagnosis *in vivo*; however, this technology is limited by low resolution. Grippo et al (Am J Pathol 2011, 179:610–618) used high-field-strength MR without contrast agents to visualize acini, islets, and blood vessels of *ex vivo* murine pancreata. High-field-strength MR results corresponded well with established criteria obtained by histology and the compiling of 2D images into a 3D image set. Such improvements to imaging technology may, in the future, lead to more accurate diagnoses and treatment.

A New Model for Testing Pulmonary Disease

Obliterative bronchiolitis is a life-threatening disease that may develop subsequent to lung transplantation. A new report by Xue et al (Am J Pathol 2011, 179:745–753) describes development and validation of a model that utilizes both human lung tissue and human effector cells. Lung explants from human cadavers were transplanted into NOD/SCID mice, followed by adoptive transfer of allogeneic human T cells. Three weeks after implantation, the lung tissue showed evidence of inflammatory cell infiltration, and one week later, tissue exhibited extensive damage (ie, loss of airway epithelium and obliteration of airway lumens). This model provides a promising opportunity to evaluate the ability of immunosuppressants to delay the onset of disease.

Activating Different TLRs Produces Different Outcomes in the Brain

The Toll-like receptors (TLRs) are active in the innate immune response, and each recognizes a different, specific component of bacteria or viruses. Whereas TLR7 recognizes single-strand RNA (and the agonist imiquimod) and TLR9 binds to oligonucleotides lacking methylation at CpG sites (CpG-ODN), both receptors share signaling pathway components. Butchi et al (Am J Pathol 2011, 179:783–794) examined the ability of TLR7 and TLR9 agonists to mediate neuroinflammation. Imiquimod-activated TLR7 elicited a weak inflammatory response compared to that of CpG-ODN-mediated TLR9, which effected significantly larger releases of cytokines (ie, IL-12 p40 and tumor necrosis factor) and a breakdown of the blood-CSF barrier, leading to infiltration of the CNS by peripheral cells. Choroid plexus cells are surmised to broker the increase in cytokine production brought on by TLR9 activation. These findings indicate that proper drug choice, insofar as TLR responses are concerned, is critical to ameliorating neuroinflammation.

Follistatin Improves Skeletal Muscle Healing

Fibrosis and inadequate myofiber regeneration frequently hamper recovery from skeletal muscle injury. In an effort to identify therapies that both stimulate muscle regeneration and inhibit fibrosis, Zhu et al (Am J Pathol 2011, 179:915–930) investigated follistatin, an antagonist of the TGF-β superfamily member myostatin. After skeletal muscle injury, follistatin-overexpressing transgenic mice displayed significantly greater myofiber regeneration and less fibrosis formation compared to wild-type mice. Furthermore, isolated muscle progenitor cells showed improved regeneration of dystrophin-positive myofibers when transplanted into the skeletal muscle of *mdx*/SCID mice. *In vitro*, follistatin stimulated myoblasts to express the myogenic transcription factors MyoD, Myf5, and myogenin. Thus, follistatin may be beneficial for a variety of skeletal muscle injuries and disorders, such as muscular dystrophies.

Cutting the Effect of Fat in Breast Cancer

Obesity conveys significant risk for breast cancer, and the adipocyte-expressed cytokine leptin plays a crucial role. Catalano et al (Am J Pathol 2011, 179:1030–1040) evaluated the ability of peroxisome proliferator-activated receptor-gamma (PPARγ) ligands to counteract leptin stimulatory effects on breast cancer growth. PPARγ activation prevented the development of leptin-induced MCF-7 tumor xenografts in mice and inhibited cell-cell aggregation and proliferation. PPARγ ligands also abrogated upregulated gene expression of leptin and its receptors, inhibited leptin signaling mediated by MAPK/STAT3/Akt phosphorylation, and counteracted leptin's stimulatory effects on estrogen signaling. These results highlight the possible therapeutic benefits of PPARγ ligands in the treatment of breast cancer.