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This Month in *AJP*

Novel Biomarker of Metastatic Bladder Cancer

Bladder cancer commonly metastasizes to both the lung and liver. To examine the mechanisms that regulate general or organ-specific metastasis in bladder cancer, Smith et al **(Am J Pathol 2009, 174:371–379)** repeatedly injected a bladder cancer cell line into either mouse spleen or tail vein to generate liver- or lung-specific metastatic cells, respectively. On cross-site injection, these conditioned cells continued to metastasize in an organ-specific manner. Laminin V gamma 2 (LAMC2) was shown to be up-regulated in both lung- and liver-specific cell lines, as well as in human tumors. In a panel of human bladder cancer tissues, LAMC2 levels were found to increase as a function of tumor stage; however, LAMC2 levels were inversely correlated with lymph nodal metastasis. Therefore, LAMC2 may be a novel biomarker for bladder cancer metastasis with hematogenous, but not lymphatic, dissemination.

Bone Marrow-Derived Collagen-Producing Cells in Airway Remodeling

Asthmatic airway remodeling is characterized by structural changes in the lungs such as an increase in smooth muscle mass and subendothelial fibrosis. Bone marrow-derived fibroblasts may participate in this process, as may stem cell factor, a growth and migratory factor that increases airway hyperreactivity. Dolgachev et al **(Am J Pathol, 2009 174:390–400)** hypothesized that stem cell factor was involved in the recruitment and differentiation of bone marrow-derived fibroblast precursors in a murine model of asthma. The number of bone marrow-derived fibroblasts significantly increased in mouse lungs after disease induction. These cells expressed the precursor molecules c-kit, CD31 receptor, and telomerase reverse transcriptase. Stem cell factor neutralization not only prevented airway remodeling, but also inhibited the migration of bone marrow-derived fibroblasts to the lung. These results suggest that stem cell factor plays a key role in recruiting bone marrow-derived fibroblasts to the lung during the process of airway remodeling.

Staphylococcus aureus β-Toxin Causes Lung Injury

Pneumonia caused by *Staphylococcus aureus* is characterized by severe inflammation and exaggerated neutrophil immigration, resulting in lung injury. To identify the mechanisms governing this extreme immune response, Hayashida et al **(Am J Pathol 2009, 174:509–518)** examined the role of *S. aureus* β-toxin in the induction of lung injury in mice. Mice infected with β-toxin-deficient *S. aureus* exhibited attenuated lung injury, as determined by levels of neutrophil migration, vascular leakage into lung tissue, and protein exudation into the airway, compared with mice infected with wild-type *S. aureus*. In addition, *S. aureus* β-toxin induced lung injury in wild-type but not neutropenic mice or mice that lack sphingomyelinase activity. The authors also examined the role of syndecan-1, a heparin sulfate proteoglycan expressed on alveolar epithelial cells that when shed facilitates neutrophil migration into lung tissue. Syndecan-1-deficient mice were also protected from β-toxin-induced lung injury. These results indicate that *S. aureus* β-toxin may play a critical role in *S. aureus*-induced lung injury through both sphingomyelinase activity and downstream effects on syndecan-1.

Rosiglitazone Attenuates Murine Scleroderma

Scleroderma, or systemic sclerosis, results from excessive collagen accumulation in the skin. Transforming growth factor-β (TGF-β), an anti-inflammatory molecule, is a key mediator of this process; however, systemic inhibition of TGF-β may result in spontaneous autoimmunity. Because peroxisome proliferator activated receptor-γ (PPAR-γ) has been implicated in the fibrotic process, Wu et al **(Am J Pathol 2009, 174:519–533)** treated mice that had bleomycin-induced skin inflammation with Rosiglitazone, a potent PPAR-γ agonist. Rosiglitazone-treated mice had lower levels of skin inflammation, reduced up-regulation of collagen expression, and fewer myofibroblasts than control bleomycin-induced mice. Rosiglitazone blocked TGF-β-mediated fibroblast activation and restored innate PPAR-γ expression, which is decreased by TGF-β signaling. These results implicate PPAR-γ ligands as putative therapeutic agents for scleroderma.

Loss of Glycinergic Innervation in Amyotropic Lateral Sclerosis (ALS) Mice

Transgenic mice overexpressing mutated human SOD1 (G93A-SOD1), a Cu/Zn superoxide dismutase, provide a model for amyotrophic lateral sclerosis, a neurological

disease characterized by loss of motoneurons in humans. Motoneuron hyperexcitability, which leads to excitotoxicity, may be caused by either excessive synaptic excitation or insufficient synaptic inhibition. Chang and Martin **(Am J Pathol 2009, 174:574–585)** hypothesized that inhibitory innervation of spinal motoneurons is abnormal in G93A-SOD1 mice. Glycinergic, but not GABAergic or cholinergic, terminals were reduced in G91A-SOD1 mice, as determined by quantitative confocal microscopy. This loss of inhibitory innervation preceded structural evidence for motoneuron degeneration. Therefore, loss of inhibitory glycinergic innervation may contribute to motoneuron hyperexcitability and degeneration in amyotrophic lateral sclerosis.

Constitutive Lactation and Mammary Tumor Prevention

Extended lactation protects against human mammary tumor development. Sotgia et al **(Am J Pathol 2009, 174:613–629)** demonstrated that mice deficient in caveolin-3, which is expressed in mammary myoepithelial cells, had a constitutive lactation phenotype. Caveolin-3-deficient mammary glands underwent lobulo-alveolar hyperplasia, similar to that observed during pregnancy/lactation, and expressed gene transcripts associated with lactation, as determined by genome-wide transcription profiling. Specifically, three transcription factors that regulate lactation in the mammary gland, Elf5, Stat5a, and c-Myc, were up-regulated in caveolin-3-deficient mice. In addition, β-casein and whey acidic protein were expressed in mammary glands in these mice, indicating milk production. Notably, caveolin-3-deficient mice were also protected against mammary tumor formation and lung metastasis. These mice, therefore, represent a model of constitutive lactation that may be useful in studying the prevention or treatment of human breast cancers, and caveolin-3 may represent a specific new therapeutic target.