

This Month in AJP

Monitoring Acute Kidney Injury

Acute kidney injury lacks effective treatment, except for supportive renal replacement therapy such as dialysis. Novel biomarkers therefore need to be developed to identify injury at early time points as well as to estimate the severity of the damage. Negishi et al (**Am J Pathol 2009, 174: 1154–1159**) examined whether levels of urinary L-type fatty acid-binding protein (L-FABP) could be used to monitor acute kidney injury. Levels of L-FABP correlated with the level of acute kidney injury at significantly earlier time points than levels of conventional renal markers such as blood urea nitrogen or urinary *N*-acetyl-D-glucosaminidase. In addition, L-FABP showed better correlation than blood urea nitrogen or *N*-acetyl-D-glucosaminidase with final histological injury scores, especially at early time points. L-FABP thus represents a better choice than conventional renal markers for evaluating early acute kidney injury.

Unfolded Protein Response Is Activated in Pretangle Neurons in Alzheimer's Disease

The unfolded protein response protects cells from the toxic effects of accumulated misfolded proteins; however, prolonged activation of the unfolded protein response, such as in Alzheimer's disease, may lead to cell death. Hoozemans et al (**Am J Pathol 2009, 174: 1241–1251**) hypothesized that the unfolded protein response contributed to neurodegeneration in Alzheimer's disease partially through its effects on the accumulation of hyperphosphorylated tau, a major component of intracellular neurofibrillary tangles in patients with Alzheimer's disease. Unfolded protein response markers co-localized with tau accumulation and expression of GSK-3 β , which phosphorylates tau, in hippocampi from patients with Alzheimer's disease but not from control patients. Unfolded protein response-related proteins were expressed in pretangle hippocampal neurons but were absent in tangle neurons. The unfolded protein response may, therefore, be pathogenic in neurodegeneration in Alzheimer's disease.

Bacterial Lymphostatin Disrupts Epithelial Barrier Function

Enteric Gram-negative bacteria can breach the intestinal epithelial barrier and cause systemic infection. Lymphostatin, a toxin produced by Gram-negative bacteria in-

cluding enteropathogenic *Escheria coli* and *Citrobacter rodentium*, has been associated with bacterial virulence. To determine whether lymphostatin affects epithelial barrier integrity, Babbitt et al (**Am J Pathol 2009, 174: 1347–1357**) generated strains of *C. rodentium* with mutations in either the glucosyltransferase (*CrGIM21*) or protease (*CrPrM5*) domain of lymphostatin. Whereas wild-type *C. rodentium* disrupted epithelial barrier function, *CrGIM21* and *CrPrM5* had reduced effects on tight junctions and adherens junctions, respectively. These effects were mediated through modulation of Rho-GTPase activities. These data suggest that lymphostatin may be a strong target candidate for treatment of enteric Gram-negative bacteria.

NF- κ B Activation Tracking Detects Early Autoimmunity

Early, preclinical, detection of autoimmunity is imperative to assess new therapeutic strategies. Inflammatory responses activate NF- κ B, making it a prime candidate to track autoimmune activity. Zangani et al (**Am J Pathol 2009, 174: 1358–1367**) used a bioluminescence reporter system to label NF- κ B activation in a mouse model of systemic autoimmunity with features of systemic lupus erythematosus. They found that NF- κ B activation signals were present in affected organs several weeks before either autoantibody production or the clinical manifestations of disease. The bioluminescent signal intensity correlated with disease progression. NF- κ B tracking may therefore provide a new tool in the evaluation of early autoimmune therapies.

Mouse Model of Human Psoriasis

Psoriasis is a chronic inflammatory disease characterized by epidermal hyperplasia, leukocyte infiltration, increased angiogenesis, and increased presence of inflammatory cytokines. The study of psoriasis has been limited, however, because of the absence of a mouse model that adequately reproduces these symptoms. Overexpression of the angiopoietin receptor Tie-2 in epithelial cells and keratinocytes has provided the best psoriasis model to date. To determine whether Tie-2 overexpression in epithelial cells or keratinocytes resulted in the psoriasis phenotype, Wolfram et al (**Am J Pathol 2009, 174: 1443–1458**) engineered two new mouse models in which Tie-2 expression was limited to either epithelial cells or keratinocytes. Only the keratinocyte-restricted

Tie-2 mice developed a cutaneous psoriasiform phenotype, and the symptoms were reduced by either repression of the transgene or treatment with cyclosporin A, a common psoriasis therapy. Keratinocyte-restricted Tie-2 mice, therefore, may serve as an animal model for human psoriasis.

Galectin-3 Regulates Prostate Cancer Progression

Down-regulation of galectin-3, a β -galactosidase-binding protein, has been reported to correlate with neoplastic progression in prostate cancer; however, galectin-3 up-

regulation has also been linked to tumorigenicity in a number of other tumor types. Wang et al (***Am J Pathol* 2009, 174: 1515–1523**) examined the role of galectin-3 during prostate cancer progression. They found that galectin-3 was cleaved during prostate cancer progression. In addition, galectin-3 siRNA knockdown led to reduced cell migration, invasion, cell proliferation, anchorage-independent colony formation, and tumor growth in a mouse model. In a human prostate cancer cell line, galectin-3 reduction was associated with metastatic events such as reduced cell migration, cell invasion, and suppression of matrix metalloproteinase-2 and -9. Thus, cleaved galectin-3 may serve as a diagnostic marker and therapeutic target for prostate cancer progression.