This Month in AJP

Modeling Neurofibromas and Malignant Peripheral Nerve Sheath Tumors

Malignant peripheral nerve sheath tumors (MPNSTs) are highly aggressive Schwann cell-derived sarcomas, but an accurate animal model is lacking. Kazmi et al (Am J Pathol 2013, 182:646–667) tested the usefulness of P0-GGFβ3 transgenic mice overexpressing neuregulin-1 in Schwann cells as a model for neurofibroma-MPNST progression. Histology linked developed sarcomas to neurofibromas and revealed Ras hyperactivation and defects in the p19ARF-Mdm-2, p16INK4A-cyclin D/CDK4-Rb, and p27Kip1/CDK2 pathways. Array comparative genomic hybridization identified multiple known and previously unknown chromosomal gains and losses affecting driver genes. This study establishes P0-GGFβ3 mice as a robust model for identification of novel genes driving neurofibroma and MPNST pathogenesis.

LXRs Prevent Diabetic Renal Damage

Dyslipidemia, a frequent component of the metabolic disorder of diabetic patients, contributes to organ damage. Kiss et al (Am J Pathol 2013, 182:727–741) assessed the anti-inflammatory and anti-fibrotic effects of liver X receptor (LXR) activation on renal damage in hyperlipidemic-hyperglycemic mice. LXR stimulation by the agonist GW3965 upregulated genes involved in cholesterol efflux, downregulated proinflammatory/profibrotic cytokines, and reduced xanthine oxidoreductase and nitrotyrosine. GW3965 or LXRα overexpression in vitro significantly suppressed glycated or acetylated LDL-induced cytokines and reactive oxygen species. Transgenic LXRα expression in macrophages ameliorated hyperlipidemic-hyperglycemic nephropathy in vivo. Thus, modulating macrophage-mediated injury by LXRs may be a relevant target for treating diabetic nephropathy.

MUC18 Amplifies Lung Inflammation

Bacterial infection exacerbates lung disease via excessive inflammation, but the underlying mechanisms remain poorly understood. Wu et al (Am J Pathol 2013, 182:819–827) explored the function of transmembrane glycoprotein MUC18 in lung inflammatory responses to Mycoplasma pneumoniae (Mp) infection. Lung Mp infection in MUC18−/− mice demonstrated a decrease in lung pro-inflammatory cytokines and neutrophil recruitment and cytokine production by alveolar macrophages. Studies in primary alveolar macrophage cultures revealed amplified MUC18-mediated pro-inflammatory responses, in part through enhanced activation of NF-kB. These data suggest a pro-inflammatory role of MUC18 whereby alveolar macrophages sensitize diseased lungs to invading pathogens.

Convergent Replication of Mouse Synthetic Prion Strains

Prion diseases, such as Creutzfeldt-Jakob disease (CJD) in humans, are characterized by the aberrant folding of endogenous proteins into self-propagating pathogenic conformers. Ghemmaghami et al (Am J Pathol 2013, 182:866–874) investigated the nature of synthetic prion transformation by infecting mice with a conformationally diverse set of amyloids and serially passaging the resulting prion strains. Monitoring biochemical and biological properties of the adapting strain at each passage showed that the physicochemical properties of each synthetic prion strain gradually changed upon serial propagation until attaining a common adapted state with shared physicochemical characteristics. These results demonstrate that synthetic prions can assume multiple intermediate conformations before converting into one conformation optimized for in vivo propagation.

Understanding Glucose Homeostasis in Chagas Disease

Chagas disease, caused by Trypanosoma cruzi, is an important cause of morbidity and mortality primarily from cardiac dysfunction, though other organs are also damaged. Nagajyothi et al (Am J Pathol 2013, 182:886–894) studied the relationship between T. cruzi infection, Chagas disease, and host glucose homeostasis in mice. T. cruzi infection induced inflammation and parasitism of the pancreas including the pancreatic β-cell. Furthermore, mice demonstrated defective hepatic gluconeogenesis. These data establish a complex, multi-tissue relationship between T. cruzi infection, Chagas disease, and host glucose homeostasis.