This Month in AJP

New Biomarker for Muscle Damage

The striated muscle-specific protein Xin localizes to the myotendinous junction in skeletal muscle but is observed throughout skeletal muscle fibers and within satellite cells in injured muscle. Using immunofluorescent staining, Nilsson et al (Am J Pathol 2013, 183:1703–1709) analyzed Xin in skeletal muscle from 47 subjects with various forms of myopathy. Xin immunoreactivity correlated positively and significantly with the severity of muscle damage, regardless of myopathy type. Xin immunoreactivity increased 24 hours post-exercise in damaged muscle fibers and within the activated muscle satellite cells of healthy individuals subjected to damaging eccentric exercise. Thus, Xin represents a useful marker of damaged muscle regardless of etiology and may be a suitable outcome measure of disease progression and treatment effects in clinical trials.

EP1 Deletion Is Protective in Diabetes

COX-2-derived PGE$_2$ signaling through specific prostaglandin E receptors (EPs) may promote renal dysfunction in hypertension and/or diabetes. Thibodeau et al (Am J Pathol 2013, 183:1789–1802) hypothesized that specific deletion of EP1 (gene PTGER1) would attenuate diabetic nephropathy-induced tissue damage in diabetic mice. In two diabetic mouse models lacking EP1, albuminuria, mesangial matrix expansion, and glomerular hypertrophy were each blunted compared to wild-type counterparts. EP1 activation contributed to diabetic nephropathy progression at several locations including podocytes, proximal tubule, and the vasculature, further implicating COX-derived PGE$_2$ in renal disease. Targeting renal EP1 may represent a worthy therapeutic goal to circumvent adverse effects associated with current COX-modulating drugs.

Hepatitis C and Alcohol Exacerbate Liver Injury

The transcription factor FOXO3 is an important component of the antioxidant stress response that can be altered by hepatitis C virus (HCV). Using FOXO3$^{-/-}$ mice, Tunurbaatar et al (Am J Pathol 2013, 183:1803–1814) examined the effects of HCV and alcohol separately and in combination on FOXO3 activity during alcoholic liver injury. Loss of FOXO3 expression in mice resulted in a phenotype in which alcohol consumption caused severe liver injury similar to that of human alcoholic hepatitis. Although HCV and alcohol each activated FOXO3, the HCV-alcohol combination suppressed it, decreased the expression of cytoprotective genes, and led to liver injury. FOXO3 pathway modulation may represent a therapeutic approach for HCV-alcohol–induced liver injury.

Periodontal Bone Loss through Apoptosis

Periodontal disease, the most common osteolytic disease, is significantly increased by diabetes mellitus. To determine if bacterial infection induces bone loss in diabetic animals via enhanced apoptosis, Pacios et al (Am J Pathol 2013, 183:1928–1935) used a caspase-3/7 inhibitor in a type 2 diabetic rat model of periodontal disease induced by bacterial infection. Bacterial infection doubled the number of TNF-$\alpha$–expressing cells and increased apoptotic cells adjacent to bone by 10-fold. Caspase inhibitor treatment blocked apoptosis, increased the number of osteoclasts, and eroded bone surface. Yet, the inhibition of apoptosis increased net bone area by increasing new bone formation, osteoblast numbers, and bone coupling. This is the first demonstration that apoptosis significantly contributes to periodontal bone loss in bacteria-induced periodontitis.

Impact of Differential Methylation in Prostate Cancer

Genome hypermethylation represents a critical mechanism in human malignancies by inactivating tumor suppressor genes and promoting tumorigenesis. Yu et al (Am J Pathol 2013, 183:1960–1970) performed whole genome methylation sequencing on 13 prostate samples, including five prostate tumors (T), four matched benign prostate tissues adjacent to tumor (AT), and four age-matched organ donor (OD) prostate tissues. Unique methylation profiles distinguished the T, AT, and OD samples. Greater than 95% of alterations of genome methylation occurred in sequences outside CpG islands. The numbers of differential methylation sequences, however, were dramatically reduced when the analysis was focused only on CpG islands. These findings suggest that potential functionally significant methylation information lies outside of CpG islands.