



This Month in *AJP*

Managing Fatty Degeneration in Skeletal Muscle

There are no safe drugs to prevent fatty degeneration in skeletal muscle. Using human platelet-derived growth factor receptor α (PDGFR α)-positive mesenchymal progenitors, a source of ectopic adipocytes in skeletal muscle, Kasai et al (***Am J Pathol*, 187:2627–2634**) screened existing drugs to identify potential candidate(s). Upon screening, promethazine hydrochloride (PH) safely inhibited adipogenesis dose-dependently, prevented expression of adipogenic markers, and suppressed phosphorylation of cyclic AMP response element binding protein, a primary regulator of adipogenesis. Using lineage tracing in a mouse model of tendon rupture with intramuscular fat deposition, PDGFR α^+ cells were found to be a source of ectopic adipocytes. Treatment of injured mice with PH significantly suppressed formation of ectopic adipocytes. PH may prevent loss of muscle function resulting from fatty degeneration.

Modeling Pancreatitis

Development of treatments for pancreatitis suffers due to lack of validation studies in human tissue. Using human acini isolated from cadaveric pancreata from organ donors, Lugea et al (***Am J Pathol*, 187:2726–2743**) performed *ex vivo* pancreatitis studies. Human cadaveric pancreatic acini maintained physiological functions and showed similar pathological responses and organellar disorders with pancreatitis-causing treatments as observed in rodent acini. Enriched acini from donors of diverse ethnicity showed similar proteome profiles. Human cadaveric pancreatic acini may help advance our understanding of pancreatitis to develop effective treatments.

Understanding Acetaminophen Hepatotoxicity

Despite implications of miR-122 in acetaminophen (APAP)-induced acute liver failure (ALF), its *in vivo* role in APAP toxicity remains elusive. Using liver-specific miR-122 knockout mice (LKO), Chowdhary et al (***Am J Pathol*, 187:2758–2774**) studied its role in APAP-induced ALF. miR-122 is down-regulated in liver biopsies of ALF patients and in APAP-treated mice. APAP overdose suppressed miR-122 expression, and loss of miR-122 sensitized mice to APAP overdose. Hepatic levels of APAP-toxicifying enzymes Cyp1A2 and Cyp2E1 were increased in miR-122 LKO mice. miR-122 modulated Cyp1A2

expression through Cyp1A2 trans-activators aryl hydrocarbon receptor and mediator 1, and miR-122 target CCCTC-binding factor. Replenishing miR-122 suppressed APAP-induced hepatotoxicity in miR-122 LKO mice. miR-122 depletion sensitized differentiated human HepaRG cells to APAP toxicity. miR-122 may be targeted in APAP-induced ALF.

Characterizing Human Fetal Membrane Microfractures

Our understanding of structural alterations (microfractures) in amniochorionic membranes in normal and pathological pregnancies is limited. Richardson et al (***Am J Pathol*, 187:2821–2830**) visualized novel cellular and extracellular matrix level microfractures in term and preterm human fetal membranes. Three-dimensional multilayer representations of the surface organization of amniochorionic membranes were generated using a combination of multiphoton autofluorescence and second harmonic generation microscopy. Number and morphometry of microfractures between term and preterm; labor and no labor; and oxidative stress (cigarette smoke extract) and control were compared. Increased microfractures were observed in preterm tissue and in response to oxidative stress. Studying microfractures may improve our understanding of their role in amniochorionic membrane dysfunctions.

Understanding Neurodegeneration in Neuroinflammation

The role of angiotensin (Ang) II in modulating the expression of toll-like receptors (TLRs) during experimental autoimmune encephalomyelitis (EAE) remains unexplored. Guo et al (***Am J Pathol*, 187:2876–2885**) studied the effects of Ang II receptor antagonist candesartan on optic neuritis in the EAE mouse model. Ang II concentration was increased in the early phase of EAE. Oral administration of candesartan markedly reduced demyelination of the optic nerve and spinal cord and decreased retinal ganglion cell loss and visual impairment in EAE mice. In astrocytes, Ang II up-regulated the expression of TLR4 via the NF- κ B pathway. Ang II treatment increased lipopolysaccharide-induced production of monocyte chemoattractant protein 1 in astrocytes, which was suppressed by pretreatment with candesartan. The renin-Ang system–NF- κ B–TLR4 axis may be targeted to manage neurodegeneration in neuroinflammatory diseases.