This Month in AJP

Brain Injury Induces Liver Inflammation

Traumatic brain injury (TBI) induces an acute-phase response (APR) that is managed by the liver. Using a male mouse TBI model of controlled cortical impact injury (CCI), Villapl et al (Am J Pathol 2015, 185:2641—2652) examined liver and plasma expression of the early APR biomarker serum amyloid A1 (SAA1). Aside from the expected immediate up-regulation of SAA1 in the liver in response to CCI, neutrophil and macrophage infiltration, apoptosis, and CXCL1 and CXCL10 chemokine levels were increased. A delayed increase in mRNA expression of angiotensin II receptor (AT1R) was also noted. Treatment with the AT1R antagonist telmisartan 1 hour post injury significantly decreased liver SAA1 levels and CXCL10 mRNA expression after 3 days, without affecting expression of CXCL1 or the number of apoptotic cells or infiltrating leukocytes. Blocking AT1R with telmisartan could be therapeutic for selected hepatic APR following TBI.

MAGED1 Negatively Regulates Bone Remodeling

Despite being implicated in bone biology, the adaptor protein MAGED1 remains only a hypothetical player in bone remodeling. To explore this role, Liu et al (Am J Pathol 2015, 185:2653—2667) studied the bone phenotype in Maged1-deficient mice. Maged1 deficiency caused significant osteopenia with a clear decrease in bone density and worsening of trabecular architecture. In vivo and in vitro analyses revealed that MAGED1 deficiency resulted in increased bone resorption and bone formation, with the former outpacing the latter. Further studying the novel negative bone remodeling regulator MAGED1 will improve our understanding of this complex process.

TMIGD1 Protects against Renal Oxidative Damage

Renal epithelial cell survival dictates the outcome of both acute kidney injury and chronic kidney diseases; thus, discernment of its molecular regulators is a significant goal. Arafa et al (Am J Pathol 2015, 185:2757—2767) identified and characterized a new adhesion molecule, transmembrane and immunoglobulin domain containing 1 (TMIGD1). Highly conserved in humans and other species, TMIGD1 is expressed in kidney tubular epithelial cells. TMIGD1 promotes cell survival; regulates cell migration, morphology, transepithelial electrical resistance, and permeability; and protects cells during oxidative stress and nutrient deprivation. TMIGD1 expression is reduced in models of chronic kidney disease and ischemia reperfusion. The novel cell adhesion molecule TMIGD1 protects renal epithelial cells from oxidative injury, expanding our knowledge of the molecular mechanisms involved.

Effects of Prenatal Acetaminophen

The effects of the commonly used over-the-counter medication acetaminophen (APAP) during pregnancy have not been comprehensively evaluated, but a link to asthma risk has been reported. Using an established mouse model, Thiele et al (Am J Pathol 2015, 185:2805—2818) studied the effects of APAP on maternal and fetal development. Administering a high APAP dose (beyond the recommended range) resulted in liver toxicity in all mice. In pregnant dams, the high-APAP dose significantly increased mature dendritic cell and regulatory T cell levels in uterus-draining lymph nodes. APAP dose-dependently decreased plasma progesterone levels in pregnant dams and caused placental damage. In the fetus, APAP reduced weight in a dose-dependent manner, lowered hepatic hematopoietic stem cell count at high dose, and delayed T-cell development in general. Prenatal APAP interferes with normal pregnancy by affecting fetal maturation and immune development, which may have long-lasting consequences such as increased risk for asthma.

Isoform Expression Patterns in Muscular Dystrophies

For unknown reasons, some muscles are able to escape the dystrophic effects of disease-causing mutations. Huovinen et al (Am J Pathol 2015, 185:2833—2842) hypothesized that the variable muscle-specific expression of certain exons may result in different phenotypes in genetic muscular dystrophies. The expression patterns of 57 muscle-specific genes and their exons in different human adult lower limb skeletal muscles were studied molecularly. Anatomically different muscles exhibited significantly variable isoform and gene expression levels. In particular, the variable expression of TTN and MYH7 correlated with the selective pattern of dystrophic change observed in two autosomal dominant titinopathies and one autosomal dominant myosinopathy. These data emphasize the need to explore relative gene silencing of the mutant allele in the management of dominant muscle disorders.