This Month in AJP

**Bile Acids Contribute to Hepatic Encephalopathy**

Elevated bile acids following liver injury lead to various complications; however, their role in hepatic encephalopathy remains unclear. Using an acute liver failure mouse model, McMillin et al (Am J Pathol 2016, 186:312–323) considered the role of increased bile acids in neurological complications. Bile acid content in the frontal cortex increased during acute liver failure, with levels correlating with the degree of hepatic encephalopathy. Modulating total bile acid levels and composition in the serum altered neurological decline. Farnesoid X receptor (FXR)–mediated signaling contributed to the neurological impairment. Altering bile acid content or FXR signaling in the brain may alleviate the neurological consequences associated with acute liver failure.

**mTORC1 Deficiency Causes Male Infertility**

The common immunosuppressant rapamycin, which inhibits mammalian target of rapamycin complex 1 (mTORC1), may cause male reduced or loss of fertility, but the mechanism remains unclear. Using a genetic mouse model of mTORC1 deficiency, Schell et al (Am J Pathol 2016, 186:324–336) investigated the underlying mechanism of infertility. The mTORC1 complex was selectively inactivated in epithelial derivatives of the Wolffian duct, resulting in infertility with severe decrease in sperm number and motility. Regression of epididymis and seminal vesicles was augmented with age. Histological analysis revealed strong epididymal epithelial damage, many spermiophages, and decreased translational activity in seminal vesicle epithelial cells. mTORC1 deficiency in nontesticular male reproductive tissue drives rapamycin-associated male infertility.

**Understanding HIV-Associated Nephropathy**

HIV-induced podocyte pyroptosis—induced by Nod-like receptor protein 3 (NLRP3) inflammasome complexes—contributes toward the development and progression of HIV-associated nephropathy (HIVAN). Haque et al (Am J Pathol 2016, 186:347–358) studied the role of HIV in podocyte NLRP3 inflammasome formation in HIVAN. HIV-1 promoted IL-1β production and caspase-1 activation in kidney cells of HIV-transgenic mice. In vitro, HIV enhanced protein expression of components of the NLRP3 inflammasome complex as well as IL-1β production. HIV promoted podocyte pyroptosis in a dose- and time-dependent manner, and this cell death could be blocked using inhibitors of caspase-1, reactive oxygen species, and NLRP3.

**Plaque Toxicity Accrues over Time in Alzheimer Disease**

The changes in plaque-associated pathology with the progression of Alzheimer disease (AD) are unclear. Serrano-Pozo et al (Am J Pathol 2016, 186:375–384) hypothesized that plaque-related local toxicity accrues with the advancement of AD. Neuronal, astrocytic, and microglial markers of local plaque-associated damage were examined in a large series of autopsied AD and healthy subjects using unbiased quantitative neuropathological and statistical methods. The markers of plaque toxicity changed throughout the course of AD, leading to an overall temporal increase in local plaque-associated damage, independent of the APOEε4 allele. Developing alternate disease-modifying therapies to manage plaque-associated injury may delay AD progression.

**NELL-1 Enhances BMP-2 Osteogenesis**

Nel-like molecule-1 (NELL-1) and bone morphogenetic protein-2 (BMP-2) regulate bone growth and repair. Using a rat femoral segmental defect (FSD) model and cell cultures, Shen et al (Am J Pathol 2016, 186:419–434) studied cross talk of these osteoinductive molecules. NELL-1 promoted BMP-2–induced osteogenesis and prevented BMP-2–induced adipogenesis via canonical Wnt signaling. Combining NELL-1 with BMP-2 treatment may significantly improve outcomes of current clinical bone regeneration therapies as well as engender novel treatment approaches for osteoporotic bone loss.