This Month in AJP

FAEES Are Protective in Acute Pancreatitis

Fatty acid ethyl esters (FAEEs) have been implicated in alcoholic acute pancreatitis (AP). Patel et al (Am J Pathol 2016, 186:874–884) explored the toxic effects of fatty acids and the derivative FAEEs on AP severity. FAEEs induced larger increases in cytosolic calcium, mitochondrial depolarization, and necroapoptosis in vitro acinar cells than the parent fatty acids at equimolar concentrations. In an established pancreatitis model, lipolysis of candidate unsaturated triglyceride worsened AP and increased mortality compared to its FAEE. In vivo comparison of local and systemic injury in rats confirmed that FAEEs were less toxic than the parent fatty acids, suggesting FAEEs exert a protective role in alcoholics.

Polarity Switching Drives Liver Metastasis of Colorectal Cancer

Little is known about the role of dysregulated polarity in cancer. Okuyama et al (Am J Pathol 2016, 186:899–911) investigated the mechanisms of polarity switching in cancer tissue–originated spheroids and its role in liver metastasis of colorectal cancer. Spheroids were cultured in suspension or in type I collagen gel. Two types of highly interchangeable polarities (apical-in and apical-out) were observed. In patients, circulating metastatic cancer cells exhibited both polarities whereas primary and metastatic tumors displayed apical-in polarity. The polarity switch was critical in an experimental mouse liver metastasis model. Inhibitors of Src and dynamin attenuated the polarity switch in vitro and significantly decreased liver metastasis in vivo. Quick polarity switching and subsequent adhesion appears necessary for liver metastasis.

Serotonin Tilts Th17/Treg Balance in Arthritis

The role of the neurotransmitter serotonin in the onset of rheumatoid arthritis (RA) is controversial. Chabbi-Achergli et al (Am J Pathol 2016, 186:927–937) studied the impact of its deficiency during the clinical expression of arthritis in an established collagen-induced arthritis (CIA) mouse model. Progression of arthritis, bone destruction, and inflammatory response were studied upon inducing arthritis in wild-type and tryptophan hydroxylase1–deficient mice, which have reduced levels of peripheral serotonin. Serotonin exerted an anti-inflammatory action during CIA onset and progression, and it modified osteoclastogenesis and the underlying immune response by dampening Th17 and increasing regulatory T cells. Serotonin represents a key therapeutic target to reestablish a proper immune response in RA.

Understanding the Evolution of Mammalian Synthetic Prions

Understanding fatal neurodegenerative prion diseases is limited by the ability to reproduce and test prion protein (PrP) molecular transformation in vitro from the normal cellular (PrPC) to the infectious scrapie (PrPSc) isoform. Makarava et al (Am J Pathol 2016, 186:1006–1014) investigated the formation of synthetic prions, and their ability to evolve into pathogenic entities during propagation, to test the deformed templating model. The inoculation of noninfectious purified recombinant hamster PrPC into transgenic mice that overexpressed hamster PrPC resulted in the accumulation of atypical proteinase K–resistant form (PrPres) in some animals. The conversion of atypical PrPres to PrPSc was independent of the substrate concentration. Atypical PrPres and PrPSc competed during the propagation process in vitro but not in vivo, suggesting that the rate of deformed templating is independent of PrPC expression levels.

PLVAP Controls Blood-Retinal Barrier Loss

Plasmalemma vesicle-associated protein (PLVAP) in retinal capillaries is linked with loss of blood-retinal barrier (BRB) properties and correlates with increased vascular permeability in diabetic macular edema. Wisniewska-Kruk et al (Am J Pathol 2016, 186:1044–1054) investigated the role of PLVAP in mediating the loss of inner BRB (iBRB) integrity following exposure to vascular endothelial growth factor (VEGF)-induced permeability. Decreasing the levels of PLVAP significantly prevented VEGF-mediated effects on the iBRB in vitro and in vivo. The suppression of PLVAP expression prevented VEGF-induced caveolae formation. PLVAP is an essential cofactor in VEGF-induced BRB permeability and a potential therapeutic target for diabetic macular edema therapy.