This Month in AJP

Neuropitin 2 Deficiency Prolongs Inflammation

Neuropitin 2 (NRP2), vascular endothelial growth factor A (VEGFA) and semaphorin 3F (SEMA3F) receptor, are expressed by vascular and lymphatic endothelia. Based on the behavior of another VEGF receptor, Mucka et al (Am J Pathol 2016, 2803–2812) hypothesized that NRP2 loss in mice would attenuate induced increases in vascular permeability. Surprisingly, Nrp2−/− mice showed twofold greater vascular permeability compared to wild-type littermates in delayed-type hypersensitivity responses. SEMA3F administration to wild-type mice dampened VEGFA-induced vascular permeability, implicating the loss of endogenous SEMA3F signaling in the phenotype of the Nrp2-deficient animals. The deficient mice also lacked superficial lymphatic capillaries, contributing to prolonged lymphedema after inflammation. The SEMA3F/NRP2 axis should be further explored in human inflammatory disorders and lymphedema.

Heme Oxygenase Reduces Complement-Mediated Glomerular Injury

Decay accelerating factor (DAF) protects against complement-mediated glomerular injury. To evaluate the role of its putative regulator heme oxygenase (HO)-1, Detsika et al (Am J Pathol 2016, 2833–2845) generated HO-1 deficient rats and rats with HO-1 overexpression in DAF-expressing glomerular epithelial cells (GEC). HO-1 regulated constitutive DAF expression. GEC-targeted HO-1 overexpression reduced complement deposition and proteinuria in anti-GBM antibody–mediated injury. The natural HO substrate hemin induced, attenuated, and augmented glomerular DAF in control, HO-1−/− deficient, and HO-1−overexpressing rats, respectively. Hemin analogs showed similar results as well as reduced complement C3b deposition, which was reversed using DAF-blocking antibody. HO-1 up-regulates glomerular DAF and minimizes complement deposition and associated injury.

Modeling Repetitive Head Trauma

Studies on repetitive mild traumatic brain injury (rmTBI) are limited by the available animal models. To gain insights into the severity and frequency of head injury required to trigger adverse behavioral outcomes, Briggs et al (Am J Pathol 2016, 2869–2886) administered 30 head impacts to lightly anesthetized, completely unrestrained mice, using two different weights over extended time. rmTBI impaired sensorimotor and neurological performance; elicited depression-like behavior and a persistent reactive gliosis; reduced cognitive performance; resulted in chronic traumatic encephalopathy— and Alzheimer disease—like neuropathology, diffuse axonal injury, and increased oligodendrocyte lineage cells; and caused white matter thinning and reductions in myelin. The outcomes evolved over time as a function of impact force. This promising rmTBI mouse model may help improve our understanding of rmTBI and related disorders.

Circadian Clock Regulators Contribute to Alcoholic Liver Disease

The nuclear receptor small heterodimer partner (SHP), a key component of the liver circadian clock machinery, has been implicated in non-alcoholic fatty liver disease. Yang et al (Am J Pathol 2016, 2909–2920) studied its role in alcoholic fatty liver disease (ALD). Steatosis was monitored over time in a mouse model of acute alcohol-induced liver injury. Knockdown of another modulator of circadian rhythm, REV-ERBα, prevented steatosis in response to ethanol in Shp−/− mice, indicating cross talk between SHP and REV-ERBα. In vitro, REV-ERBα activated transcription of the gene encoding C/EBP homologous protein (CHOP), a marker of endoplasmic reticulum stress, which was repressed by SHP. SHP and REVERBα thus contribute to ALD by regulating the rhythmic expression of CHOP.

Neuropeptide Y May Predict Neuroblastoma Relapse

Neuropeptide Y (NPY), a sympathetic neurotransmitter expressed in the pediatric malignancy neuroblastoma (NB), is a potential therapeutic target. Galli et al (Am J Pathol 2016, 3040–3053) further investigated its clinical relevance and utility in NB biology. Expression of NPY and its receptors was compared in tumor RNA, tumor tissues, patient sera, and tumor tissues from an established mouse model. Increase in serum NPY levels corresponded to adverse NB presentation and prognosis as well as relapse. Enhanced immunoreactivity of the receptor Y5R and both NPY and Y5R marked angioinvasive patient tumor cells and NB cells in the mouse model, respectively. NPY is a minimally invasive biomarker for monitoring NB progression.