This Month in AJP

Managing Post-Transplant Acute Kidney Injury

The levels of microRNA miR-182-5p increase in post-transplant acute kidney injury (AKI). To further study its involvement in AKI, Wilflingseder et al (Am J Pathol 2017, 187:70-79) inhibited its renal expression with specific antisense oligonucleotides (ASO). ASO-mediated knockdown of miR-182-5p in rats resulted in improved renal function and less morphological damage after ischemia-reperfusion injury. ASO effectiveness was further validated in an ex vivo perfused pig kidney model, which closely resembles the human allograft setting. Targeting miR-182-5p may help reduce AKI in the context of human renal transplants.

Understanding Liver Fibrosis

Receptor tyrosine kinases (RTK) regulate hepatic stellate cell (HSC) function and liver fibrosis. Wang et al (Am J Pathol 2017, 187:134-145) investigated the role of the GTPase dynamin-2 (Dyn2) in RTK-mediated HSC activation and liver fibrosis. HSC expressing Dyn2K44A, which contains a GTPase activity-disrupting point mutation, displayed increased mRNA and protein levels of sphingosine kinase-1 (SK1), an enzyme previously implicated in the pathogenesis of fibrosis. Further, Dyn2K44A promoted both AKT phosphorylation and HSC migration in an SK1 dependent manner, and mice expressing Dyn2K44A in HSC had increased fibrosis after liver injury. Dyn2K44A promotes HSC activation and liver fibrosis in part via up-regulation of SK1 transcription and HSC migration.

Interleukin-34 Expression Is Inhibited in Rheumatoid Arthritis

Interleukin-34 (IL-34) has been implicated in rheumatoid arthritis (RA). Chemel et al (Am J Pathol 2017, 187:156-162) investigated the impact of transforming growth factor (TGF)-β family members—TGF-β1 and bone morphogenetic protein (BMP)-2—on IL-34 expression in RA. IL-34, TGF-β1, and BMP-2 were found in synovial fluids from RA patients, with a positive correlation between the levels of IL-34 and TGF-β1. TGF-β1 and BMP2 down-regulated the baseline expression of IL-34 mRNA in human synovial fibroblasts and murine mesenchymal stem cells in a dose- and time-dependent manner through ALK5 and ALK1 pathways, respectively. Also, TGF-β1 and BMP-2 antagonized TNFα-induced IL34 gene expression. TGF-β1 and BMP-2 may help control inflammation and reverse bone erosion in RA.

Modeling Salmonella Meningitis

Our understanding of the progression of Salmonella meningitis is limited by the lack of relevant animal models. Bauler et al (Am J Pathol 2017, 187:187-199) examined the ability of Salmonella enterica serovar Typhimurium to cause meningitis in highly susceptible Nramp1−/− and more resistant Nramp1+/− mice following the natural route of infection. In both strains, oral administration of the bacteria caused meningitis with detectable levels of Salmonella in the central nervous system (CNS) and an influx of inflammatory cells in the brain. Some Nramp1+/− mice that developed clinical neurological disease showed characteristic pathological features of human Salmonella meningitis. Though Nramp1 is not essential for Salmonella entry into the CNS or neuroinflammation, it may still contribute to that entry as well as the severity of meningitis.

Targeting Invasive Bladder Cancer

Human bladder cancer specimens from patients with more aggressive types of tumors have reduced levels of argininosuccinate synthetase 1 (ASS1), a key cellular enzyme for arginine synthesis. Sahu et al (Am J Pathol 2017, 187:200-213) therefore investigated the impact of extracellular arginine degradation on tumor cell biology. When exposed to an arginine-degrading enzyme, selected bladder cancer cell lines showed a dose-dependent decrease in colony formation, viability, and cell cycle transit. These changes were accompanied by biochemical alterations linked to autophagy and stress signaling and could be reversed by ASS1 overexpression. Therapeutic ADI-PEG 20 arginine deiminase (ADI) arrested tumor growth in selected mouse xenografts. ADI-PEG 20 may be an effective treatment for bladder cancers with reduced expression of ASS1.