This Month in AJP

Modeling COVID-19

The lack of relevant animal models has limited our understanding of the pathobiology of coronavirus disease 2019 (COVID-19) as well as testing possible interventions. Using aged African green monkeys (AGMs) infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Blair et al (Am J Pathol 2021, 274–282) modeled acute respiratory distress syndrome (ARDS), which is a common symptom in severely ill COVID-19 patients, and often a cause of death. Eight aged AGMs were exposed to SARS-CoV-2, and they exhibited mild to severe COVID-19 with increased levels of plasma IL-6, a predictive biomarker and potential therapeutic target. In two AGMs, the disease progressed to ARDS, and these AGMs exhibited pathologic lesions and disease reported in severely ill COVID-19 human patients. Aged AGMs may help model severe COVID-19 to study the pathobiology and underlying mechanisms and explore treatment options.

Treating Age-Related Dry Eye

The link between oxidative stress and inflammation in the lacrimal gland (LG) is unclear. Using mouse models, de Souza et al (Am J Pathol 2021, 294–308) explored the role of age-related oxidative stress in LG inflammation. An age-dependent increase in the infiltration of immune cells was observed in the LG. The number of goblet cells was significantly lower in aged mice compared with young mice. LG inflammation was increased and correlated with an increased level of oxidative stress markers. Lack of nuclear factor erythroid-derived-2—related factor 2 (Nrf2), a regulator of antioxidant genes, increased inflammation in middle-aged Nrf2-deficient mice compared with control mice. Inflammation in LG decreased, and the number of goblet cells increased, when normal aged mice were fed Nrf2-inducing diet compared with standard diet. Oxidative stress pathways may be targeted to treat age-related dry eye.

Understanding Liver Microstructure

Integrins are critical for hepatocyte—extracellular matrix (ECM) interactions. Using inducible integrin β1—deficient mice and liver cell cultures, Masuzaki et al (Am J Pathol 2021, 309–319) studied the role of integrin β1 in liver microstructure development and restructuring after liver injury. Integrin β1 was found to be critical for microscopic patterning of the liver, bile canaliculi formation in developing liver, re-establishment of liver architecture after liver injury, and inhibition of transforming growth factor-β1 signaling from hepatocytes during liver maturation. Integrin β1 is critical in maintaining liver architecture; disrupting hepatocyte-ECM interaction may be sufficient to drive fibrosis.

Targeting Melanoma

The ubiquitin-conjugating enzyme RAD6B stabilizes β-catenin, and its depletion reverses epithelial-to-mesenchymal transition in breast cancer cells. Using gene editing and a small-molecule inhibitor of RAD6, Sarma et al (Am J Pathol 2021, 368–384) studied the role of RAD6B in the development and progression of melanoma. Limiting RAD6 inhibited melanoma cell proliferation. Loss or inhibition of RAD6B in metastatic melanoma cells down-regulated β-catenin signaling and downstream effectors, and decreased cell migration/invasion, tumor growth, and lung metastasis. RAD6B may be targeted to treat melanoma.

Understanding T-Cell Trafficking to Inflamed Lymph Nodes

The role of the GTPase R-Ras in high endothelial venule (HEV) function is unclear. Sawada et al (Am J Pathol 2021, 396–414) explored this role using Rras knockout (KO) mice and cell cultures. Endothelial cell—specific inducible Rras KO mice were generated, and pathogen-induced naïve T-cell trafficking to lymph nodes was studied. On immune challenge, HEVs transiently up-regulated R-Ras in mice in a tumor necrosis factor—dependent manner. Vascular R-Ras is critical in regulating trans-endothelial migration of naïve T cells into the inflamed lymph nodes.