This Month in AJP

Understanding Cutaneous Leishmaniasis

MicroRNA 155 (miR155) promotes CD4$^+$ T-helper cell 1 (Th1) response and interferon gamma (IFN-γ) production; however, it is not critical to control infection caused by Leishmania donovani ($L$. donovani). Using miR155 deficient (miR155$^{-/-}$) mice, Varikuti et al (Am J Pathol 2021, 191:809-816) studied the role of miR155 in cutaneous leishmaniasis (CL) resulting from $L$. major infection. miR155$^{-/-}$ mice contained infection significantly faster compared to wild type mice by impairing Th2 response and promoting Th1 immune response. In vitro analysis confirmed attenuated dendritic cell (DC) activation and function upon miR155 deficiency. miR155 may promote vulnerability to $L$. major-induced CL by promoting Th2 response and reducing DC activity.

Understanding Diabetic Lung Injury

The mechanisms underlying diabetic lung injury are unclear. Using mouse models, Wang, Hu, and He et al (Am J Pathol 2021, 191:838-856) studied pulmonary fibrotic changes in diabetic lungs. The NF-κB signaling pathway was activated in the lungs in these models and its constitutive activation increased pulmonary alveolar wall thickening and fibrotic changes in the lungs. Restoration of microbiome reversed the activation of NF-κB signaling and associated fibrotic changes. NF-κB signaling pathway is critical in diabetic lung injury.

Managing Autosomal Dominant Polycystic Kidney Disease

DNA damage and changes in DNA damage response (DDR) signaling may mediate focal kidney cyst formation in autosomal dominant polycystic kidney disease (ADPKD). Zhang et al (Am J Pathol 2021, 191:902-920) hypothesized that the markers of DNA damage and DDR signaling increase in human and experimental ADPKD. Changes in transcriptomes were analyzed using normal and end-stage human ADPKD tissue as well as in a mouse model of cystic disease at different time points. DDR signaling was found to be impaired in human ADPKD and in the early stages of murine ADPKD. Cyst growth increased upon DNA damage in vitro. Blocking DDR pathway in ADPKD may help manage kidney cyst growth.

Targeting Human Hepatocellular Carcinoma

The role of adenomatous polyposis coli (APC), a tumor suppressor and a negative regulator of β-catenin and Wnt signaling pathway, in hepatocarcinogenesis is unclear. Using human hepatocellular carcinoma (HCC) and hepatoblastoma (HB) samples, Zhang et al (Am J Pathol 2021, 191:930-946) studied APC mutations and their expression patterns. Using mouse models, they also studied the effect of loss of Apc on liver tumor development in vivo, either alone or in combination with other oncogenes. Though the loss of Apc alone did not drive liver tumor formation, it synergized with a few activated oncogenes to induce hepatocarcinogenesis, via β-catenin and its downstream targets. Blocking functional β-catenin pathway prevented liver tumor formation. Targeting the Wnt/β-catenin pathway may benefit HCC patients with loss of function APC mutations.

Treating Diabetes

NF-κB inhibition helps mitigate microvascular complications like neuropathy. Using a preclinical type 1 diabetic mouse model, Homme et al (Am J Pathol 2021, 191:947-964) studied the effect of long-term NF-κB inhibition on retinal vasculopathy. Inhibition of NF-κB by a small molecule inhibitor resulted in decreased basal glucose levels, intraocular pressure as well as key inflammatory molecules, and a significant mitigation of vascular remodeling and microaneurysms in diabetic mice compared to the wild type mice. Decreasing inflammation may help protect the diabetic retina and its vasculature.