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This Month in *AJP*

Managing Pulmonary Hypertension

The role of Kv11.1 potassium channels in the lung is unclear. Shults et al (**Am J Pathol 2020, 48–56**) studied the expression of Kv11.1 in healthy human and rat lung tissues and in humans with chronic obstructive pulmonary disease (COPD)-associated pulmonary hypertension (PH) and rats with pulmonary arterial hypertension (PAH). Kv11.1 channels are amply expressed in and confined to the large pulmonary arteries (PAs) of healthy lung tissues. This expression increases in human lungs affected by COPD-associated PH and in mouse lungs with PAH, with detectable expression in small PAs. The Kv11.1 channel expression in small PAs follows the time course of pulmonary vascular remodeling in PAH in rats. Blocking Kv11.1 channel in PAH rats inhibited PAH-associated pulmonary vascular remodeling. Kv11.1 channels may be therapeutically targeted in PH treatment.

Suppressing Dry Eye Disease

Despite implications in dry eye disease (DED), the role of the neuropeptide substance P (SP) in its pathogenesis is unclear. Using cultured cells and a mouse model of DED, Yu et al (**Am J Pathol 2020, 125–133**) studied this role. SP is constitutively expressed at the ocular surface. SP, primarily produced from the trigeminal ganglion neurons in DED, augments the maturation of bone-marrow–derived dendritic cells *in vitro*. Antagonizing SP signaling abrogates this effect *in vitro* and *in vivo*. Blocking SP signaling may suppress ocular surface disease.

Dissecting Endometriotic Fibrosis

Myocardial infarction studies revealed that transcription factor 21 (*TCF21*) is an upstream regulatory gene of periostin. Ganieva et al (**Am J Pathol 2020, 145–157**) studied the role of *TCF21* and periostin in the development of endometriosis. Archived tissue sections from normal endometrium and various samples from endometriosis lesions were studied. TCF21 regulates the expression of periostin, and both periostin and TCF21 are up-regulated in endometriosis lesions, especially in samples from women with deep endometriosis. *TCF21* may serve as a biomarker and a therapeutic target in endometriosis management.

Delaying Nephronophthisis Type 7

Mutations in *GLIS2*, which encodes a nuclear transcription factor, cause nephronophthisis (NPHP) type 7. By genetically altering *Glis2* alone and in combination with components of the DNA-damage response pathway in mice, Jin et al (**Am J Pathol 2020, 176–189**) examined the underlying mechanisms. Suppressing Glis2 activates toll-like receptor 2/interleukin receptor 1 (TLR2/IL-1R) signaling. A combined loss of Glis2 and TLR2 activity improves the regenerative potential of tubular cells. Inhibition of TLR2/IL-1R signaling in conjunction with senolytic therapy may delay NPHP type 7 progression.

Understanding Fibroblast Plasticity

The myofibroblast-like cancer-associated fibroblasts (CAFs) are critical to the growth and metastasis of cancer. Using mouse melanoma tumor and spheroid tissue culture models, Tsang et al (**Am J Pathol 2020, 206–221**) studied the underlying mechanisms. As anticipated, the stem cell transcription factor Sox2 is induced in stromal CAFs derived from Col1a2-expressing fibroblasts. The differentiation of skin progenitor cells into myofibroblast is CCN2-dependent. CCN2 may be therapeutically targeted to modulate fibroblast plasticity and manage melanoma.

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