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This Month in *AJP*

Healing Corneal Defects

The role of the aquaporin AQP5 in corneal epithelial wound healing and nerve regeneration is unclear. Using CRISPR/Cas9 technology, Liu et al (**Am J Pathol 2021, 1974–1985**) generated transgenic *Aqp5* knockout mice to study this role. The transgenic mice showed impaired corneal epithelial wound healing due to decreased cell proliferation and a significant delay in both corneal epithelial and nerve regeneration. Inducing AQP5 may help accelerate corneal epithelial regeneration and promote the regeneration of corneal epithelial nerve fibers in corneal defects.

Understanding Osteoarthritis Progression

The role of hyaluronan (HA)-binding protein involved in HA depolymerization (HYBID) in osteoarthritis (OA) progression is unclear. Using osteoarthritis mouse models lacking the HA depolymerase Hybid, Momoeda et al (**Am J Pathol 2021, 1986–1998**) studied this role. High molecular weight HA accumulated in OA joint tissues *in vivo* in the absence of Hybid. Cartilage destruction and osteophyte formation were suppressed in *Hybid*$^{-/-}$ mice. Inhibiting HYBID may help manage OA progression.

Managing Renal Cell Carcinoma

Development of effective treatments for renal cell carcinoma (RCC) is limited by our lack of understanding of cancer cell–intrinsic mTOR-mediated pathways. Using clear cell RCC (ccRCC) cell lines, Lee et al (**Am J Pathol 2021, 1999–2008**) studied the effect of mTOR regulation on transcription factor E3 (TFE3) and PD-L1 in RCC. TFE3 overexpression correlated with increased expression of PD-L1 as well as enhanced mTOR activity, and the knockdown of TFE3 correlated with reduced PD-L1 expression. mTOR inhibition enhanced TFE3 expression with concomitant increased expression of PD-L1. Both the immune checkpoint and mTOR pathways may be targeted to manage RCC.

Modeling Myelodysplastic Syndromes

Aberrant miRNA expression is associated with a myelodysplastic syndrome (MDS) phenotype. Using a stable knockdown of miR-378-3p in transfected human hematopoietic stem cells and promyelocytic leukemia cell lines, Wang et al (**Am J Pathol 2021, 2009–2022**) generated a novel model for MDS. This model showed characteristics of MDS including aberrant signaling, immunophenotypic changes, morphologic dysplasia, and aberrant growth and function, which could be reversed with azacytidine. The model also mimicked aberrant signal transduction in response to stimulation as seen in MDS patient samples. The novel miRNA-based cell line model of MDS may help understand underlying biology and identify novel therapies for MDS.

Treating Metastatic Malignant Melanoma

The role of intussusceptive angiogenesis—characterized by intravascular pillars—in human tumors is unclear. Using human malignant melanomas, patient-derived melanoma xenografts in mice (PDX), and a transgenic mouse model, Pandita et al (**Am J Pathol 2021, 2023–2038**) studied this role. Intravascular pillars were observed in human metastases, were rare in PDXs, and absent in transgenic mice. MMP9 mRNA expression was higher in human metastases; higher matrix metallopeptidase-9 (MMP9) protein expression and macrophage and T cell infiltration was observed near intravascular pillars. *In vitro*, MMP chemical inhibition blocked pillar formation. Blocking MMP-9 may help manage intravascular pillars as well as metastatic melanoma.

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