This Month in AJP

Blocking Psoriatic Arthritis

Our understanding of the pathogenesis of psoriatic arthritis (PsA), a chronic autoimmune disease that affects millions of individuals, is limited by the lack of relevant animal models. Dantas et al (Am J Pathol 2017, 187:2388—2398) generated a mouse model in which PsA is triggered by an inducible human tumor necrosis factor (hTNF) transgene. Knocking out the gene encoding four and a half LIM domain protein 2 (FHL2), a transcriptional cofactor that modulates cellular signaling pathways, in the PsA mouse model exacerbated disease and promoted infiltration of inflammatory leukocytes into lesions in the skin and digits. This increased severity was accompanied by higher levels of soluble hTNF, the shedding of which was impeded by FHL2 in vitro. FHL2 is an anti-inflammatory protein that plays a key role in PsA development.

Preventing Kidney Fibrosis

There is a lack of effective options for treating fibrosis of chronic kidney disease (CKD). To identify therapeutic targets, Schwalm et al (Am J Pathol 2017, 187:2413—2429) induced fibrosis in mice via unilateral ureteral obstruction. Sphingosine kinase-2 (SPHK2) was up-regulated in kidney tubules of mice upon induction of fibrosis. Mice deficient in SPHK2 had an attenuated fibrotic response, which was accompanied by greater expression of anti-fibrotic SMAD7 and higher levels of sphingosine. Conversely, renal fibrosis was exacerbated in mice overexpressing human SPHK2. In primary kidney fibroblasts, sphingosine reduced fibrotic changes elicited by transforming growth factor-β. SPHK2 may represent a new target for therapeutic intervention.

Treating Hepatic Insufficiency Safely

Sobetirome (GC-1) mimics the mitogenic activity of thyroid hormone T3 on hepatocytes but has fewer side effects, making it a potential agent for promoting liver regeneration. A caveat is that GC-1 acts through Wnt/β-catenin signaling, and abnormal activation of β-catenin is seen in some hepatocellular carcinomas (HCC). Using in vitro and in vivo approaches, Puliga et al (Am J Pathol 2017, 187:2473—2485) evaluated whether GC-1 promotes development or growth of HCC. Exposure of cultured HCC cells to GC-1 did not affect β-catenin activity, regardless of whether the cells harbored wild-type or mutated pro-oncogenic β-catenin. In a mouse model of HCC driven in part by mutated β-catenin, GC-1 reduced tumor burden and proliferation of tumor cells. GC-1 may be a safe treatment for stimulating liver regeneration in patients with chronic hepatic insufficiency.

Understanding Lung Cancer Progression

Activated leukocyte cell adhesion molecule (ALCAM) has been linked to invasion and metastasis of tumor cells, but whether its presence on tumor stromal cells contributes to cancer progression is unknown. To address this question, Willrodt et al (Am J Pathol 2017, 187:2558—2569) examined behavior of cancer cell lines in ALCAM-deficient mice. When three cell lines were delivered intravenously, absence of ALCAM in the recipients dramatically curtailed growth of tumors in the lungs. In two cases, homing to the lung was unaffected. In contrast, Lewis lung carcinoma cells displayed reduced homing in the ALCAM-deficient mice and were impaired in spontaneous metastasis to the lung when implanted subcutaneously. Diminished tumor growth was associated with impaired angiogenesis. ALCAM on stromal cells in the tumor microenvironment plays a pivotal role in growth of lung cancers and can contribute to metastasis.

Preserving Vision in Macular Degeneration

Choroidal neovascularization (CNV) leads to vision loss in age-related macular degeneration (AMD). The contribution of transforming growth factor-β (TGF-β) to CNV was dissected by Schlecht et al (Am J Pathol 2017, 187:2570—2589) through generation of mice with induced, conditional deletion of TGF-β signaling in various components of the eye. Deletion of signaling in the entire eye of young mice led to CNV, accompanied by degeneration of photoreceptors, multilayering of the retinal pigment epithelium (RPE), and accumulation of macrophages. Deletion of TGF-β signaling in only the RPE had no obvious effects. In contrast, ablation specific to the vascular endothelium of the eye mimicked the phenotype seen when TGF-β signaling was eliminated in the entire eye. TGF-β signaling, particularly in endothelium, is key to development of CNV and may offer targets for new therapies to prevent vision loss in patients with AMD.