This Month in AJP

Periostin and Exocrine Pancreatic Tissue

Despite known functions of the extracellular matrix molecule periostin in chronic pancreatitis and pancreatic cancer, its role in acute pancreatitis remains unclear. Hausmann et al (Am J Pathol 2016, 186:24–31) studied its function in pancreatic exocrine regeneration following severe acute pancreatitis (AP). Severe AP was induced in adult mice with and without global periostin ablation. Detailed histological analysis revealed similar pancreatitis severity in the acute inflammatory phase in all mice. However, in periostin-deficient mice the recovery of the exocrine pancreas was vastly impaired, and acinar-to-adipocyte differentiation as well as expression levels of pancreatic and acinar differentiation markers were disturbed. Periostin regulates acinar cell fate decision and restores pancreatic tissue integrity following AP.

Granzyme B Mediates Cardiac Fibrosis

The serine protease Granzyme B (GzmB) contributes to several fibrosis-related cellular processes, but a direct link with cardiac fibrosis is missing. Using fibrotic human hearts and an established angiotensin II (Ang II)—induced cardiac fibrosis mouse model, Shen et al (Am J Pathol 2016, 186:87–100) studied the role of GzmB in the pathogenesis of cardiac fibrosis. GzmB was up-regulated in both fibrotic human and murine hearts. In mice, GzmB deficiency protected against Ang II—induced cardiac hypertrophy and cardiac fibrosis—independent of perforin—by reducing microhemorrhage, inflammation, and fibroblast accumulation. In vitro, GzmB directly cleaved the endothelial junction protein VE-cadherin, disrupting barrier function. Targeting extracellular GzmB may halt the progression of cardiac fibrosis.

Mast Cell—Derived Histamine Promotes Cholangiocarcinoma

Mast cells (MCs) contribute to the pathogenesis of cholangiocarcinoma (CCA) by releasing inflammatory factors that support tumor progression. Using in vitro and in vivo models, Johnson et al (Am J Pathol 2016, 186:123–133) dissected the role of MCs in the pathophysiology of CCA. MC infiltration into the CCA microenvironment and the expression of MC markers were observed in human biopsies and mouse tumors. Blocking MC-derived histamine decreased tumor growth, proliferation, angiogenesis, epithelial-mesenchymal transition, and extracellular matrix degradation via inhibition of c-Kit/stem cell factor. Preventing MC migration may be an important target for CCA therapy.

IL-10 Regulates Inflammatory Corneal Lymphangiogenesis

How the anti-inflammatory cytokine IL-10 regulates inflammatory lymphangiogenesis is unknown. Using an established mouse model, Hos et al (Am J Pathol 2016, 186:159–171) determined the impact of IL-10 on inflammatory corneal lymphangiogenesis and the resolution of corneal inflammation. IL-10 was detected in inflamed, but not healthy, corneas and was expressed by infiltrating macrophages. In vitro IL-10 stimulation up-regulated the expression of pro-lymphangiogenic vascular endothelial growth factor-C in macrophages but did not affect lymphatic endothelial cells. In vivo IL-10 deficiency reduced corneal lymphangiogenesis and prolonged corneal inflammation. Local treatment with IL-10 promoted lymphangiogenesis and faster egress of macrophages from inflamed corneas. IL-10 may be useful therapeutically to resolve pathological inflammation in the cornea.

Aβ Precedes p-Tau in Alzheimer Disease Synapses

The detailed time course of amyloid-β (Aβ) and hyperphosphorylated tau (p-tau) accumulation in Alzheimer disease (AD) patient synapses is unclear. Bilousova et al (Am J Pathol 2016, 186:185–198) investigated this sequence using patient samples and a transgenic rat model. Aβ and p-tau were quantified across AD disease stages (including non-demented high AD—related pathology controls) in parietal cortex. Aβ accumulated in the earliest plaque stages as well as in late-stage AD dementia whereas p-tau appeared essentially in late-stage disease. Synapse-associated soluble oligomers of Aβ were linked to the onset of dementia. p-tau was elevated in individual Aβ-positive synaptosomes in early AD, arguing for an amyloid cascade hypothesis driving p-tau accumulation.