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This Month in *AJP*

The Role of Pericytes in Diabetic Retinopathy

Both type 1 and type 2 diabetes patients are at risk of diabetic retinopathy, but the relative contribution of specific cellular components to the pathobiology of diabetic retinopathy remains undefined. Valdez et al (**Am J Pathol 2014, 184:2618–2626**) addressed this issue using an inducible model of pericyte loss in nondiabetic mice conditionally expressing a diphtheria toxin receptor in mural cells to examine the acute effects of pericyte loss on adult retinal microvasculature. Five days after administering diphtheria toxin in these adult mice, retinal vasculature exhibited changes similar to those observed in diabetic patients, including microaneurysms and increased vascular permeability. These results suggest that pericyte cell loss is sufficient to trigger retinal microvascular degeneration and that pericyte protection, rescue, or replacement may be a viable therapeutic target.

Three-Probe Test Detects Prostate Cancer Progression

Sensitive and specific tests to distinguish indolent versus aggressive prostate cancers are lacking. Heselmeyer-Haddad et al (**Am J Pathol 2014, 184:2671–2686**) assessed previously identified genetic markers to understand genomic alteration dynamics in patients with or without progression after radical prostatectomy. No differences were observed in the percentage of cells with prostate cancer-specific *TMPRSS2-ERG* fusion between samples with or without progression. Tumors from patients who progressed had more chromosomal gains and losses and showed a higher degree of selection for a predominant clonal pattern. *PTEN* loss was the most frequent aberration in progressors, followed by *TBL1XR1* gain. *MYC* gain was observed in one progressor tumor, which was the only lesion with an *ERG* gain but no *TMPRSS2-ERG* fusion. Thus, a probe set consisting of *PTEN*, *MYC,* and *TBL1XR1* may detect progressors with high specificity and sensitivity in a routine pathology setting.

Tsp1 Deficiency Delays Renal Failure Onset

Thombospondin-1 (Tsp1), a multifunctional matricellular protein, promotes chronic kidney disease progression. To explore the mechanisms of Tsp1 action, Zeisberg et al (**Am J Pathol 2014, 184:2687–2698**) compared chronic kidney disease progression in *Col4A3* knockout mice with that of *Col4A3;Tsp1* double-knockout mice. Tsp1 absence significantly delayed the decline of excretory kidney function. Disease progression was predominantly associated with fibrosis and inflammation in *Col4A3* knockout and *Col4A3;Tsp1* double-knockout mice, respectively. Altered disease progression was due to impaired activation of latent transforming growth factor-β1 activation in the absence of Tsp1 *in vivo* and *in vitro*. Therapeutic strategies should target both fibrosis and inflammation as they are independent entities, each contributing to expansion of the interstitium and decline of renal function.

Cathepsin E Promotes Pulmonary Emphysema

The molecular mechanisms of emphysema, a major subset of chronic obstructive pulmonary disease, remain poorly defined. Because cathepsins have been implicated in mediating alveolar destruction, Zhang et al (**Am J Pathol 2014, 184:2730–2741**) examined their role in lung disease. Human chronic obstructive pulmonary disease lung tissues had markedly increased cathepsin E in the epithelium. Transgenic mice overexpressing cathepsin E in epithelia exhibited increased levels of E3 ubiquitin ligase parkin and mitochondrial fission protein dynamin-related protein 1 in addition to caspase activation/apoptosis and ultimately loss of lung parenchyma resembling emphysema. *In vitro* or *in vivo* inhibition of dynamin-related protein 1 with a small molecule inhibitor prevented cathepsin E–induced apoptosis and emphysema. These findings highlight a novel role of cathepsin E and mitochondrial fission in the pathogenesis of chronic obstructive pulmonary disease.

Hypertension Alters Calcium Homeostasis in Skeletal Muscle

The mechanisms underlying the development of hypertension-associated skeletal muscle pathology are poorly defined. Liantonio et al (**Am J Pathol 2014, 184:2803–2815**) assessed whether calcium homeostasis, a biomarker of muscle function, is altered in the muscles of spontaneously hypertensive rats. Hypertension caused a phenotype-dependent dysregulation of calcium homeostasis; the resting intracellular calcium of leg muscles of spontaneously hypertensive rats was differently altered with respect to the related muscles of normotensive Wistar-Kyoto rats. Soleus muscles of spontaneously hypertensive rats showed reduced activity of the sarcoplasmic reticulum and decreased sarcolemmal calcium permeability at rest and after store-operated calcium entry activation. The expression levels of some store-operated calcium entry components, excitability, and resting chloride conductance were also altered. These findings identify druggable targets for the treatment of muscle weakness affecting hypertensive patients.

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