This Month in AJP

Treating Macular Degeneration

Choroidal neovascularization can lead to blindness in patients with age-related macular degeneration (AMD), but its pathogenesis has not been well defined. Feng et al (Am J Pathol 2017, 187:2208–2221) explored the role of pro-inflammatory Toll-like receptor 2 (TLR2) in AMD. Retinal pigment epithelium (RPE) in eyes of humans and mice strongly expressed TLR2, and nuclear localization of its downstream target NF-kB was increased in eyes from patients with advanced AMD. In cultured human RPE, TLR2 ligands stimulated production of pro-inflammatory cytokines. Antagonism of TLR2 reduced the number and size of lesions in a mouse model of choroidal neovascularization, and this beneficial effect was enhanced by simultaneous treatment directed against vascular endothelial growth factor receptor 2. Targeting TLR2 may be a novel approach for reducing blindness in patients with AMD.

Dissecting Alcoholic Liver Disease

A minority of chronic, heavy drinkers develop alcoholic liver disease (ALD), underscoring the multifactorial causation of this global health problem. Warner et al (Am J Pathol 2017, 187:2232–2245) explored the contribution of dietary linoleic acid (LA) to ALD. Mice fed alcohol and a diet high in unsaturated fats (including LA) showed greater liver injury, inflammation, and steatosis compared to mice given alcohol and a diet rich in saturated fats. They also had higher plasma levels of oxidized LA metabolites, one of which provoked expression of pro-inflammatory cytokines by a mouse macrophage cell line. Liver injury in mice lacking 12/15-lipoxygenase, which oxidizes LA, was less severe than in wild-type animals when the two groups were administered alcohol and a diet high in unsaturated fats. Dietary linoleic acid and its subsequent oxidation may foster progression of ALD.

Understanding Ehlers-Danlos Syndrome

Most patients with the connective tissue disorder Ehlers-Danlos syndrome (EDS) are heterozygous for null alleles of COL5A1, which encodes the α1 chain of collagen V [α1(V)]. Null alleles of COL5A2, encoding the α2(V) chain, are not known causes of human pathology. To evaluate the role of α2(V) in integrity of connective tissues, Park et al (Am J Pathol 2017, 187:2300–2311) conditionally ablated Col5a2 in postnatal mice. Ablation led to impaired growth and wound healing, skin fragility, and aggregation of collagen fibrils. Unlike in EDS, skin was not hyper-extensible, suggesting distinct functions for α1(V) and α2(V). Haploinsufficiency of Col5a2 predisposed mice to development of aortic aneurysms, rupture, and dissection, suggesting that abnormalities in α2(V) may contribute to these conditions in humans.

Preventing Pulmonary Fibrosis

Pulmonary fibrosis (PF) is an end-stage condition with limited treatment options. Thrombomodulin improves survival of patients with idiopathic PF, but the mechanism is unknown. To gain a better understanding of how thrombomodulin ameliorates PF, Fujiwara et al (Am J Pathol 2017, 187:2312–2322) studied its effects in two mouse models of the disease. Treatment of mice with human recombinant thrombomodulin lessened levels and/or gene expression of several pro-inflammatory cytokines, growth factors, and markers of fibrinolysis. Moreover, inflammation and fibrosis were reduced in lungs of treated animals. Apoptosis of lung epithelial cells was suppressed by thrombomodulin both in vitro and in vivo. In addition to its known anticoagulant and anti-inflammatory effects, thrombomodulin may also benefit patients with PF by limiting apoptosis of lung epithelium.

Suppressing Tumor Growth

Tumors stimulate formation of new blood vessels by secreting vascular endothelial growth factor A (VEGF-A). Anti-cancer agents that target VEGF-A or its receptors are in clinical use, but their modes of action are not fully understood. To identify effects of such treatments, Sitohy et al (Am J Pathol 2017, 187:2337–2347) overexpressed VEGF-A in mice to produce a tumor-like vasculature in the absence of tumor cells. Single doses of several anti-VEGF-A agents caused rapid, specific collapse of mother vessels, which are the first type of vessel to develop during tumor angiogenesis. Transcripts for endothelial nitric oxide synthase (eNOS) were highly up-regulated during formation of mother vessels. Inhibition of eNOS suppressed angiogenesis in the VEGF-A overexpression model and reduced growth of tumors. Quantifying mother vessels in human tumors may aid in identifying patients who will respond best to anti-VEGF-A therapy.