

This Month in AJP

EMT Contributes to Ocular cGVHD

Chronic graft-versus-host disease (cGVHD) of the ocular surface, which may lead to vision loss, is a serious side effect of bone marrow transplantation. cGVHD is characterized by excessive fibrosis. As epithelial-mesenchymal transition (EMT) has been implicated in fibrotic diseases, Ogawa et al (*Am J Pathol* 2009, 175:2372–2381) explored the potential role of EMT in ocular cGVHD. They observed several features of EMT in ocular cGVHD including down-regulation of adhesion molecules; up-regulation of SNAIL, a transcription factor that plays a regulatory role in EMT; up-regulation of heat shock protein 47, an EMT marker; and epithelial up-regulation of α -smooth muscle actin, a marker of mesenchymal cells. These altered cells had disrupted basal epithelia, and altered collagen bundles were observed in or near altered epithelial cells. These results indicate that EMT may be at least partially responsible for fibrotic ocular damage in patients with cGVHD.

Bacterial Lipids Enhance Autoimmunity

Porphyromonas gingivalis, a common oral bacteria in humans, produces a unique type of lipid, phosphorylated dihydroceramides (DHCs), which enhances inflammatory responses. To determine whether these lipids affect autoimmunity, Nichols et al (*Am J Pathol* 2009, 175:2430–2438) administered phosphorylated DHCs to a mouse model of multiple sclerosis, experimental autoimmune encephalomyelitis (EAE). The severity of EAE was significantly enhanced by the addition of phosphorylated DHCs, particularly by phosphorylated ethanolamine DHCs, in a Toll-like receptor 2-dependent manner. This response was independent of natural killer T cell activation; however, significantly fewer Foxp3+ T cells were present in the spines of EAE mice with phosphorylated ethanolamine DHC treatment. These data suggest that phosphorylated DHCs from common commensal bacteria may enhance autoimmunity, perhaps by acting as a Toll-like receptor 2 ligand.

Modified pro-NGF May Lead to Symptoms of Alzheimer Disease

Oxidative stress in the early stages of Alzheimer disease may modify molecules, resulting in loss or alteration of their function. A precursor to nerve growth factor (pro-NGF) is expressed at high levels in Alzheimer disease-affected individuals, and accumulation of pro-NGF may

lead to neural cell death. Kichev et al (*Am J Pathol* 2009, 175:2574–2585) showed that pro-NGF was modified by advanced glycation and lipoxidation end products (AGE/ALEs) in an Alzheimer disease stage-dependent manner and that modified pro-NGF blocked processing to mature NGF and led to neuronal cell death. Furthermore, injection of modified pro-NGF or pro-NGF derived from human patients with Alzheimer disease resulted in cognitive and learning impairment in mice, suggesting that modified pro-NGF may provide a novel pathogenic pathway for Alzheimer disease.

Genetic Abnormality in Tumor-Associated Endothelial Cells

Angiogenesis plays a key role in tumor metastasis. The endothelial cells that compose tumor-associated blood vessels were previously thought to be genetically stable, but recent evidence suggests endothelial cell aneuploidy in some tumor types. Akino et al (*Am J Pathol* 2009, 175:2657–2667) hypothesized that endothelial cells associated with human renal cell carcinoma would have cytogenetic abnormalities. They found that a portion of tumor-associated endothelial cells had aneuploidy and that many of these cells had stem cell-like characteristics (CD133⁺). Abnormal endothelial cells may therefore contribute to the pathogenesis of metastatic carcinoma.

Wnt Is Pathogenic in Diabetic Retinopathy

Diabetic retinopathy, which results from inflammation in the eye, is the leading cause of blindness in the working-age population; however, the mechanisms by which diabetes induces this inflammation remain unclear. To determine whether the Wnt signaling pathway, which is activated under numerous pathological conditions, plays a role in diabetic retinopathy, Chen et al (*Am J Pathol* 2009, 175:2676–2685) examined retinal expression levels and nuclear translocation of the Wnt signaling molecule β -catenin in human patients with diabetic retinopathy as well as in mouse models. They found high retinal expression and nuclear translocation of β -catenin as well as increased expression of the Wnt co-receptors RP5/6 (low-density lipoprotein receptor-related proteins 5 and 6) in subjects with diabetic retinopathy. Moreover, inhibition of Wnt signaling through Dickkopf homolog 1 (DKK1) ameliorated both generation of reactive oxygen species and diabetic retinopathy in these models. Wnt therefore provides a new target for diabetic retinopathy therapy.