This Month in AJP

Modeling Age-Related Macular Degeneration

A specific complement factor H (CFH) polymorphism dramatically increases the risk of age-related macular degeneration (AMD). Using a CHF-humanized Cfh−/− mouse model, Ding et al (Am J Pathol 2015, 185:29–42) characterized the role of CFH and its AMD-associated variant in disease pathogenesis. Human CFH protein inhibited cleavage of mouse complement factor 3 and factor B in plasma and eye tissues, demonstrating that human CFH regulated activation of the mouse alternative pathway. Expression of human CFH in Cfh−/− mice showed functional and structural protection of the retina, as well as improved vision, compared with Cfh−/− mice. These humanized CFH mice represent valuable tools to study the mechanisms and environmental contributors of normal and at-risk human CFH variants in a defined model system of AMD.

TRPV1 Deficiency Ameliorates ALD

The specific mechanisms behind development of alcoholic liver disease (ALD) are poorly understood, though dietary fat is an important determinant. Liu et al (Am J Pathol 2015, 185:43–54) evaluated the role of transient receptor potential vanilloid 1 (Trpv1) signaling in a mouse model of ALD. Chronic binge alcohol administration increased the levels of bioactive oxidized linoleic acid metabolites (OXLAMs), which were associated with hepatic Trpv1 up-regulation. In vitro exposure of hepatocytes to OXLAMs activated Trpv1 signal transduction. Alcohol-fed Trpv1 knockout mice exhibited levels of steatosis similar to those of wild-type mice but with reduced cytokine and chemokine expression, necrosis, and apoptosis. TRPV1 depletion also markedly blunted ethanol-mediated induction of the hepatic inflammation mediator plasminogen activator inhibitor-1. The TRPV1-OXLAM interaction supports a role for dietary lipids in ALD.

ANKRD1 Transduces Cell-Matrix Interactions in Wound Healing

Wounding and tissue injury induce strong expression of the transcriptional cofactor ankyrin repeat domain protein 1 (Ankrd1). Samaras et al (Am J Pathol 2015, 185:96–109) generated a knockout mouse to examine the specific role of Ankrd1 in cutaneous wound healing. Although global deletion of Ankrd1 did not affect mouse viability or development, Ankrd1−/− mice exhibited necrosis of ischemic skin flaps and delayed excisional wound closure due to impaired contraction. Skin fibroblasts isolated from Ankrd1−/− mice were defective in migration and contraction of three-dimensional collagen gels; these defects could be reversed on reconstitution with ANKRD1. In vitro data were consistent with in vivo wound closure studies, indicating that Ankrd1 is critical for proper cell-matrix interaction in fibroblasts.

Reevaluating Type 1 Diabetes Development

An association between recent onset type 1 diabetes and hyperexpression of human leukocyte antigen (HLA) class I on islet cells has been suggested. Skog et al (Am J Pathol 2015, 185:129–138) explored this apparent link using quantitative approaches at both protein and mRNA levels. Immunohistochemistry detected intense staining for HLA class I on the islets of subjects with recent-onset type 1 diabetes. However, quantitative analyses revealed no difference in HLA class I expression between islet and exocrine tissue, even when comparing diabetic and nondiabetic subjects. Moreover, HLA class I-specific downstream effectors were not switched on in islets from recent-onset type 1 diabetic subjects. These data suggest possible revision of the model of islet hyperexpression of HLA class I as an important step in type 1 diabetes development.

SIRT1 Governs PARK2-Mediated Mitophagy

Mice deficient in the NAD+—dependent histone deacetylase Sirt1 develop prostatic intraepithelial neoplasia (PIN) lesions. Using Sirt1−/− mice and fibroblasts, Di Sante et al (Am J Pathol 2015, 185:266–279) delineated the role of Sirt1 in PIN development and autophagy. Sirt1 deletion induced histological features of PIN such as increased cell proliferation and enhanced mitochondrial autophagy, or mitophagy. SIRT1 Sirt1 expression was reduced in prostate cancers of patients with poor prognosis. Sirt1 deletion in mice reduced superoxide dismutase 2 activity and enhanced reactive oxygen species (ROS) production. Increased ROS in Sirt1−/− mouse fibroblasts induced mitophagy via the E3 ubiquitin ligase Park2 whereas restoration of Sirt1 inhibited Park2 translocation and ROS production. SIRT1 thus functions as a tumor suppressor by inhibiting generation of ROS and reducing mitophagy.