This Month in AJP

Targeting POLR1C-Related Treacher Collins Syndrome

POLR1C mutation has been implicated in type 3 Treacher Collins syndrome (TCS), a type of rare congenital birth disorder. Using zebrafish model, Kwong et al (Am J Pathol 2018, 188:336–342) studied the time period in which polr1c is necessary for the manifestation of TCS. Photo-cleavable morpholinos were used to restore polr1c expression in deficient zebrafish at different time points [8 hours post fertilization (hpf), 16 hpf, 24 hpf, 30 hpf, and 48 hpf]. The restoration of polr1c at early developmental stage (8 hpf) rescued the TCS facial malformation phenotype. These rescued morphants showed corrected neural crest cell expression, reduced cell death, and suppression of p53 activation. Temporally targeting POLR1C may reduce the treatment time under pharmacotherapy.

Modeling Diabetic Kidney Disease and Atherosclerosis

There are no reliable type 2 diabetes (T2D) mouse models of combined diabetic kidney disease and atherosclerosis. To generate such a mouse model, Bornfeldt et al (Am J Pathol 2018, 188:343–352) used a liver-targeted adeno-associated virus to target low-density lipoprotein (LDL) receptor in control and leptin deficient (OB) mice, via overexpression of inducible degrader of the LDL receptor (IDOL). Livers of targeted OB mice showed increased serum lipids, atherosclerosis, and proteinuria. IDOL-mediated dyslipidemia exacerbated diabetic albuminuria and glomerular macrophage accumulation. This mouse model may prove useful in studying kidney disease and atherosclerosis in T2D.

DNA Repair—Related Biomarkers in Gastric Cancer

DNA repair deregulation and alcohol consumption have been implicated in gastric cancer (GC). Using human GC biopsies, Zhang et al (Am J Pathol 2018, 188:367–377) explored the prognostic values of DNA repair proteins in the context of alcohol consumption. Immunohistochemical and in situ hybridization analysis suggested TFIIB-related factor 1 (BRF1), breast cancer susceptibility gene 2 (BRCA2), and myeloperoxidase (MPO) as independent prognostic factors in GC patients, which were significantly associated with disease-free survival (DFS). BRCA1 and BRCA2 were found to be independent prognostic factors for overall survival (OS), and BRCA2 an independent unfavorable prognostic factor for DFS and OS in GC patients post—platinum-based adjuvant chemotherapy. Alcohol-mediated DNA repair—related biomarkers—BRF1, BRCA1/2, and MPO—have prognostic value in GC patients.

Understanding Lung Damage in Primary Pneumocystis Infection

Our understanding of the damage caused to the lung by commonly occurring subclinical primary Pneumocystis infection in infants remains obscure. Using a rat model, Iturra et al (Am J Pathol 2018, 188:417–431) studied long-term effects of Pneumocystis infection on lungs. Rats were naturally infected with Pneumocystis by co-habitation at birth and lungs were assessed at 45, 60, and 75 days of age. Infected lungs revealed changes in histologic features, increase in markers for TH2-type inflammatory response, and subacute fibrosis. Subclinical Pneumocystis infection induces lung disease in the immunocompetent host, which should be clinically followed over time.

Imaging Extracellular Lipids in Atherosclerotic Lesions

Advancing atherosclerotic lesions are characterized by lipid accumulation. Using multidimensional imaging, Lehti et al (Am J Pathol 2018, 188:525–538) analyzed the ultra-structure of the accumulated lipids in endarterectomized human carotid atherosclerotic plaques. Three-dimensional (3D) electron microscopy analysis followed by molecular characterization of the isolated extracellular lipoprotein particles in the plaques revealed metabolically relevant lipoprotein-derived structures, capable of inducing lipid-accumulation as well as inflammation in atherogenesis. Multidimensional imaging of the extracellular lipoprotein particles may improve our understanding of their structure-function relationships in atherogenesis.