Journal Pre-proof

This Month in *AJP*

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Generating A Single Cell Atlas of Vestibular Schwannoma

The mechanisms underlying tumor progression of vestibular schwannoma (VS) are unclear. Using single-cell RNA-seq on three clinically isolated VS samples and by performing bioinformatics analysis, Xu, Wang, and Jiang et al **(Am J Pathol, AJPA-D-22-00041)** studied these mechanisms. Analyses were performed to examine cell composition, cell type clustering, cell proliferation, and potential regulation and communication between cell types. Data suggest a microenvironmental mechanism underlying the development of VS. This preliminary cellular atlas of VS tissue may improve our understanding of VS tumor growth.

Analyzing Gastric Foveolar-Type Adenoma

The genomic features of sporadic foveolar-type adenoma (FGA) remain unclear. Using eight fresh-frozen sporadic FGA tissue samples from *Helicobacter pylori* (Hp)-naïve patients, Mishiro et al **(Am J Pathol, AJPA-D-21-00428)** studied these features. A common single nucleotide variation was observed within the DNA binding domain of the tumor suppressor gene Krüppel-like factor 4 (*KLF4*), KLF4 c.A1322C, in all cases. The transfection of mutant *KLF4* significantly suppressed the proliferation of gastric cancer cell lines compared to the wild type gene, in part through early apoptotic phase-related genes. This novel *KLF4* mutation may be responsible for the slow growth of FGA neoplasm in Hp- naïve patients.

Understanding Liver Energy Homeostasis

The miR-122 target SLC25A34 has been implicated in non-alcoholic fatty liver disease (NAFLD) and liver cancer; however, little is known about its function. Using cultured cells and by generating a hepatocyte-specific knockout (KO) mouse model, Roy et al **(Am J Pathol, AJPA-D-22-00143)** studied this role. Depletion of *Slc25a34 in vitro* increased mitochondrial biogenesis, lipid synthesis, and ADP/ATP ratio whereas *Slc25a34* overexpression had the opposite effect. SLC25A34 KO mice showed exacerbated phenotypes of NAFLD after short-term fast-food diet (FFD) feeding and improved phenotype after long-term FFD feeding. This novel mouse model may help study the hepatic damage and mitochondrial changes associated with NAFLD.

Detecting Nasopharyngeal Cancer

Nasopharyngeal cancer (NPC) screening relies on detection of serum antibodies to Epstein-Barr virus (EBV) by immunofluorescence assay (IFA), which may suffer from observer variability. To further augment pathologist assessment as well as to scale NPC screening, Samanta and Swaminathan et al **(Am J Pathol, AJPA-D-22-00056)** used a machine learning algorithm to quantitatively characterize titers of EBV early antigen based on IF cellular staining. The hybrid

model—deep learning-fuzzy inference (DeLFI)—was clinically validated; it outperformed human evaluation and closely matched human performance. DeLFI may enable accurate and scalable population screening for NPC.

Understanding Prostate Cancer Progression

Toll-like receptor 3 (TLR3) is up-regulated in some castration-resistant prostate cancers (PCa); however, its role in PCa progression is unclear. Using prostate cell lines, Muresan et al **(Am J Pathol, AJPA-D-21-00639)** studied this role. *In vitro* activation of TLR3 resulted in secretion of some cytokines as well as an up-regulation of genes responsible for cell motility, migration, and invasion, which was also confirmed *in vivo* using an orthotopic xenograft model. Targeting TLR3 with an exogenous ligand led to apoptosis, with higher toxicity in TLR3-high chemoresistant PCa cells. TLR3 may be targeted to manage PCa progression and metastasis.

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