**This Month in AJP**

**Limiting Memory Loss in Cholestasis**

The cellular mechanisms underlying cognitive symptoms in rodent bile duct ligation (BDL) models of cholestasis are unclear. Using BDL mice and human neuronal cell cultures, Gee et al (Am J Pathol 2023, 11–26) studied these mechanisms. BDL reduced spatial learning capabilities as well as exhibited cellular changes, which were partly restored by treatment with obeticholic acid (OCA)—farnesoid X receptor (FXR) agonist and a clinically approved treatment agent. OCA therapy or FXR agonism may limit cholestasis-induced neuronal senescence.

**Modeling Acute Liver Failure**

Our understanding of the mechanisms leading to liver failure following transplantation is limited by the availability of relevant animal models. Using a rat model of drug-induced acute liver failure (ALF), Jaber et al (Am J Pathol 2023, 27–38) studied these mechanisms. The treated rats exhibited symptoms that mimicked human symptoms and exhibited substantial mortality. Ectopic hepatocyte cell therapy in this injury model normalized the pathologic effects of liver injury. New animal models of ALF may offer novel opportunities for studying liver regeneration and testing potential therapeutics.

**Diagnosing Hematologic and Solid Tumors**

Cancer management and therapy varies considerably depending on the proper classification of cancer. Using artificial intelligence (AI), Zhang et al (Am J Pathol 2023, 51–59) examined the utility of targeted transcriptome for differential diagnosis of hematologic and solid tumors. RNA from control and different tumor samples were sequenced and machine learning (ML) was used for diagnosis between two classes. ML distinguished between two diagnoses with high accuracy. Combining targeted transcriptomes with AI may improve diagnosis and classification of cancers.

**Improving Prognostic Risk Profiling for Breast Cancer**

There is a need to improve prognostic risk profiling for breast cancer in women. Using conditional mouse models for genes implicated in human breast cancer, Furth et al (Am J Pathol 2023, 103–120) studied mammary tumor frequency. The genes were induced just prior to or with reproductive senescence and the induction maintained through the age of 30 months. Induction quickly resulted in a proliferative transcriptome risk signature which preceded development of mammary cancer. The risk signature mimicked the Prosigna/PAM50 human prognostic signature for early-stage human estrogen receptor α positive (ER⁺) breast cancer. Like humans, aging facilitated ER⁺ adenocarcinoma in mice. These novel mouse models may help improve prognostic risk profiling for breast cancer in women.

**Understanding the Effects of Hyperglycemia**

The effect of hyperglycemia on endothelial cell activation and the initiation and progression of atherosclerosis is unclear. Using established mouse models of atherosclerosis and human aortic endothelial cell cultures, Mastrogiacomo et al (Am J Pathol 2023, 121–133) studied these effects. High glucose levels were found to drive the initiation of lesion formation by up-regulating the expression of adhesion molecules. Regulating blood glucose levels may help manage, or even reverse, atherosclerotic cardiovascular diseases.