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This Month in *AJP*

Exploring Congenital *Trypanosoma cruzi* Transmission

Mechanistic pathways associated with *Trypanosoma cruzi* congenital transmission leading to chronic Chagas disease are unclear. Using RNA-seq, Juiz et al (**Am J Pathol 2018, 188:1345–1353**) characterized gene expression profiles of term placentas from *T. cruzi* seropositive (SP) and seronegative (SN) mothers. A gene-set association analysis was performed on placental RNAs from paired SP and SN pools, and the differentially regulated genes/pathways were identified. Inflammatory response and lymphocytic activation was increased whereas several biosynthetic processes were down-regulated. Though most fetuses from infected mothers remain uninfected, they may be affected by the protective placental response, resulting in the low rate of congenital *T. cruzi* transmission in chronic Chagas disease.

Understanding Hepatocyte-Driven Liver Regeneration

Bromodomain and extraterminal (BET) proteins regulate cholangiocyte-driven liver regeneration. Using two established animal models, Russell et al (**Am J Pathol 2018, 188:1389–1405**) studied the role of BET proteins in hepatocyte-driven liver regeneration. Injecting JQ1, a small molecule inhibitor of BET proteins, 2 or 16 hours post–partial hepatectomy in mice increased liver injury, prevented hepatocyte proliferation and reduced the levels of cell cycle regulator *Ccnd1* mRNA and Cyclin D1 protein. Hepatocyte proliferation was similarly impaired in JQ1-treated zebrafish larvae after acetaminophen-induced injury. In both models, JQ1 suppressed Wnt signaling. Clinical use of JQ1-like inhibitors should be carefully considered to avoid hampering normal liver regeneration.

Mechanistic Insights into Ichthyotic Phenotype

The mechanism behind the phenotypes in patients with *NIPAL4* (ichthyin) mutations causing autosomal recessive congenital ichthyosis (ARCI) is unknown. To understand the underlying mechanism of this skin disorder, Mauldin et al (**Am J Pathol 2018, 188:1419–1429**) analyzed a patient as well as a canine model affected with ichthyosis resulting from *NIPAL4* mutations. Loss of NIPAL4 caused abnormalities in epidermal function in both the patient and animals. Epidermal cytotoxicity likely caused permeability barrier abnormality and compromised the formation of corneocyte lipid envelope (CLE) and weakened the cornified envelopes (CEs). Topical application of acylceramide—a lipid product distal to the mutation—in animals normalized the CLE as well as reversed the abnormality in CEs; however, the clinical phenotype was improved only partially. Persistent cytotoxicity likely due to accumulation of other toxic metabolites may also contribute to ARCI pathogenesis.

Studying Hematopoietic Cell Survival

The physiological roles of *Tmem30a*, the β subunit of P4-ATPase flippase complexes that are responsible for maintaining the asymmetry of the phospholipid bilayer, are unknown in hematopoietic cells. Using a *Tmem30a* inducible knockout mouse model, Li et al (**Am J Pathol 2018, 188:1457–1468**) studied its role in the survival of cells of the hematopoietic system. Conditional deletion of *Tmem30a* in mice caused severe pancytopenia, depleted lineage-committed blood cells and hematopoietic stem cells (HSCs), and affected multiple signaling pathways in HSCs. *Tmem30a* was found to be critical for the survival of leukemia stem cells in a *BCR/ABL1*-transduced chronic myeloid leukemia (CML) mouse model. *Tmem30a* may be targeted to manage CML due to *BCR/ABL1*.

Identifying a Biomarker for Prostate Cancers

PD-L1 protein expression is used as a predictive biomarker for responsiveness to PD-1/PD-L1–targeting therapies in many cancer types; however its expression in primary prostate cancers has been reported to be variable. Using a validated PD-L1–specific antibody in a large, representative cohort of primary prostate cancers and prostate cancer metastases, Haffner et al (**Am J Pathol 2018, 188:1478–1485**) studied PD-L1 protein expression. Though PD-L1 expression was rare in primary prostate cancers, increased rates of PD-L1 positivity were observed in metastatic castrate-resistant prostate cancer (mCRPC). Patients with mCRPC may benefit from PD-1/PD-L1 targeting therapies.

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