The American Journal of Pathology, Vol. 189, No. 10, October 2019

The American Journal of
PATHOLOGY
ajp.amjpathol.org

This Month in *AJP*

Managing Colorectal Cancer

The role of KH-type splicing regulatory protein (KHSRP) in colorectal cancer (CRC) is unclear. Using a combination of *in silico*, *ex vivo*, and *in vitro* approaches, Caiazza et al (**Am J Pathol 2019, 1916–1932**) studied this role. KHSRP is expressed in the epithelial and stromal compartments of both primary and metastatic tumors, elevated in tumor tissues compared to controls, and is a prognostic indicator of worse overall survival. KHSRP increased cell proliferation *in vitro* and promoted a pro-angiogenic extracellular environment. KHSRP promotes CRC and may be therapeutically targeted to manage it.

Understanding Diabetic Retinopathy

Though lysyl oxidase propeptide (LOX-PP) promotes apoptosis in diseased tissues, its role in vascular cell loss associated with diabetic retinopathy (DR) is unclear. Using *in vivo* and *in vitro* studies, Kim et al (**Am J Pathol 2019, 1945–1952**) examined the effects of high glucose (HG) or diabetes on LOX-PP expression and function. HG increased LOX-PP expression and decreased pro-survival signals *in vitro* and *in vivo*. These observations were replicated when recombinant LOX-PP was administered *in vitro* and *in vivo*. HG-induced LOX-PP overexpression may be targeted in preventing retinal vascular cell loss associated with DR.

Resolving Inflammation after Acetaminophen Overdose

The fibrinolytic enzyme, plasmin, regulates macrophage function; however this regulation has not been studied in the context of acetaminophen (APAP). Using mouse and *in vitro* models, Roth et al (**Am J Pathol 2019, 1986–2001**) studied plasmin-mediated macrophage function upon APAP overdose. Chemical inhibition of plasmin in mice delayed the up-regulation of proinflammatory cytokines and prevented phagocytic removal of dead cells. *In vitro*, plasmin stimulated cytokine production via NF-κB. Plasmin may help resolve inflammation after APAP overdose by promoting macrophage function.

Understanding Molecular Pathogenesis of Group A *Streptococcus*

Serotype M28 group A *Streptococcus* (GAS) strains collected from human invasive infections show a higher than expected number of polymorphisms in *rocA*. Bernard et al (**Am J Pathol 2019, 2002–2018**) hypothesized that RocA polymorphisms may alter RocA function and change the global transcriptome and hence the virulence of serotype M28 GAS. RNA-seq, *in vitro* virulence factor assays, and mouse and nonhuman primate pathogenesis studies were performed on naturally-occurring clinical isolates with *rocA* polymorphisms and isogenic mutant strains to study global GAS transcriptome changes and virulence phenotype. Naturally occurring RocA polymorphisms may uniquely alter global GAS transcriptome and GAS virulence.

Modeling Human Osteomyelitis

Staphylococcus infection may cause human bacterial chondronecrosis with osteomyelitis (BCO). Using a *Staphylococcus*-induced chicken BCO model and human osteomyelitis samples, Greene et al (**Am J Pathol 2019, 2077–2089**) studied the mechanisms underlying virulence. Administration of synthetic or genetic double stranded RNA (dsRNA) induced human osteoblast cell death *in vitro*. Infection with staphylococci isolated from chicken BCO model and human samples induced DICER1-mediated up-regulation of cytotoxic dsRNA and activated NLRP3 inflammasome *in vitro*. NLRP3 inflammasome was also activated in the bones of BCO chicken and humans with osteomyelitis compared to healthy controls. The chicken BCO model may help study human osteomyelitis and test therapeutic potential of dsRNA.

https://doi.org/10.1016/j.ajpath.2019.08.001