This Month in AJP

Immuno-Metabolic Determinants in Head and Neck Squamous Cell Carcinoma

The pathogenesis of persistent neurocognitive disorders in HIV patients who undergo effective combination antiretroviral therapy (cART) is unclear. Mangus et al (Am J Pathol 2018, 188:125–134) retrospectively analyzed neuropathology in 30 simian immunodeficiency virus (SIV)-infected pigtail macaques receiving cART. The macaques developed lymphocyte-dominated central nervous system (CNS) inflammation that was distinct from original SIV encephalitis and was independent of opportunistic agents in the CNS, other viral infections, or specific treatment regimens. Although the CNS lesions mimicked uncommon immune-mediated neurologic disorders reported in treated HIV patients, other clinically observed associations and neurologic signs were missing. Abundant CNS lesions in these animals suggest that a strong or dysregulated adaptive immune response in the CNS may result in mild neurological disorders in cART-treated HIV patients.

Managing Influenza Virus Pathogenesis

Neutrophil extracellular traps (NETs) aggravate influenza pneumonia–associated lung injury. Since histones are the major protein components of NETs, Ashar et al (Am J Pathol 2018, 188:135–148) examined their role in lung pathogenesis during influenza. In mice, lethal influenza virus infection promoted widespread release of extracellular histones into the lung air space, which in turn induced cytotoxicity and microvascular thrombosis, exacerbating tissue damage. Nasal wash samples of influenza-infected patients also showed increased accumulation of extracellular histones. Treatment with a combination of antihistone antibodies and the antiviral agent oseltamivir improved lung pathology in mice challenged with a lethal dose of influenza virus. Targeting histones may ease influenza pneumonia.

Managing Optic Neuropathies

Vitamin B12 (cobalamin) deficiency results in optic neuropathies and even loss of vision; however, underlying mechanisms remain unknown. Since cobalamin and superoxide-scavenging metallocorroles share similar core structure, Chan et al (Am J Pathol 2018, 188:160–172) hypothesized that cobalamin may act as a superoxide scavenger that protects against retinal ganglion cell (RGC) death. As expected, in vitro, cobalamin scavenged superoxide in neuronal cells with enhanced superoxide production, and it improved RGC survival. Similarly, in vivo, intravitreal cobalamin significantly reduced RGC superoxide burst resulting from optic nerve transection in rats, resulting in increased RGC survival. Managing cobalamin levels may improve outcomes in patients with degenerative eye diseases.

HnRNP U Impacts Circadian Rhythms

Patients with deletion of one copy of heterogenous nuclear ribonucleoprotein U (HNRNPU) suffer from sleep disorders. Using mice with a heterozygous loss-of-function mutation in Hnrnpu (Hnrnpu+/−), Lai et al (Am J Pathol 2018, 188:173–183) studied its impact on circadian rhythms. Hnrnpu+/− mice showed disrupted rhythms in locomotor activity as well as metabolism. HnRNP U was found to regulate genes encoding neuropeptides arginine vasopressin (Avp) and vasoactive intestinal polypeptide (Vip), by binding directly to their promoters with Bmal1:Clock heterodimers. Microinfusion of Avp and Vip into free-moving Hnrnpu+/− mice partially rescued the mentioned phenotypes. HnRNP U regulates key peptides that organize daily rhythms of physiology and behavior in mammals.