This Month in AJP

Lymphatic Vessels Are Remodeled in Crohn Disease

In mice, inflammation of the intestine can result in compromised lymphatic integrity that impairs proper trafficking of dendritic cells to draining lymph nodes. To explore whether this observation translates to humans, Randolph et al (Am J Pathol, 3066–3073) examined the mesenteric lymphatic vasculature in tissue from patients with Crohn disease (CD) or control individuals without inflammatory bowel disease. Three-dimensional imaging revealed B-cell–rich aggregates that resembled tertiary lymphoid organs (TLOs) in CD specimens. These structures impinged on lymphatic collecting vessels, and B cells and innate lymphoid cells invaded the vessel walls. TLO-like structures may affect the flow of lymph in human inflammatory bowel disease, leading to persistent immune dysregulation.

HIV Interferes with Immunity to Mycobacterium tuberculosis

Coinfection with HIV is the leading risk factor for progression of infection with M. tuberculosis (Mtbt) to active tuberculosis (TB). Singh et al (Am J Pathol, 3083–3093) explored interactions between HIV and Mtbt at the cellular level by infecting human dendritic cells (DCs) with both agents. Compared to DCs infected with Mtbt alone, coinfected cells had reduced expression of HLA-DR, co-stimulatory molecules, and proinflammatory cytokines, as well as decreased autophagy. HIV also impeded processing of Mtbt antigens by DCs and subsequent presentation to T helper cells. These changes might accelerate TB progression in HIV-positive patients and should be considered when developing therapies for this cohort.

Interleukin-1β Contributes to Retinopathy of Prematurity

Retinal dysfunction has been implicated in retinopathy of prematurity (ROP)—the most common cause of visual impairment in premature neonates—as well as later complications in ROP patients. Using a mouse model of oxygen-induced retinopathy (OIR), Zhou et al (Am J Pathol, 3100–3116) studied the cytotoxic effects of IL-1β, one of the most abundant cytokines generated in the retina during OIR, on choroidal endothelium. IL-1β levels positively correlated with choroidal degeneration. IL-1β was cytotoxic to choroid in vitro, in vivo, and ex vivo. Early treatment with IL-1 receptor antagonist protected mice against OIR, resulting in life-long improvement in visual acuity. IL-1β may be a useful therapeutic target in neonates suffering from ROP.

Substance P Enhances Immunity after Brain Injury

Patients suffering from mild traumatic brain injury (mTBI) have reduced rates of pneumonia compared to patients with blunt trauma. To examine the underlying mechanisms, Hsieh et al (Am J Pathol, 3236–3245) developed a mouse model of mTBI. Injured mice survived lung infection with Pseudomonas aeruginosa better than mice that received an injury to the tail of comparable severity. Similar levels of the neuropeptide substance P were found in the plasma and lung fluids of mice with either type of injury. Blockade of substance P reversed the protective effect of mTBI, but survival of mice with tail injury was unaltered. These two models will allow further dissection of how mTBI specifically enhances innate immunity and may point the way to novel host-driven therapies to combat infections.

Sirtuin 6 and Protein Kinase CK2A1 May Predict Breast Cancer

The role of sirtuin 6 (SIRT6) in tumorigenesis is controversial. Bae et al (Am J Pathol, 3297–3315) analyzed expression of SIRT6 and a possible regulator, protein kinase CK2A1 (CSNK2A1), in 142 human breast carcinomas. Nuclear expression of SIRT6 and CSNK2A1 correlated with shorter overall and relapse-free survival. In vitro, CSNK2A1 bound to and phosphorylated SIRT6. Moreover, knockdown of SIRT6 diminished replication and invasive behavior of a breast cancer cell line, whereas overexpression promoted proliferation. SIRT6 and CSNK2A1 are thus prognostic indicators for breast cancer patients, and phosphorylation of SIRT6 by CSNK2A1 may contribute to breast cancer progression.