This Month in AJP

EPRAP Regulates Inflammation in the Brain

Prostaglandin E2 type 4 receptor—associated protein (EPRAP) suppresses macrophage activation in the periphery. Since microglial over-activation is neurotoxic, Fujikawa et al (Am J Pathol 2016, 186:1982–1988) studied the role of EPRAP in regulating brain inflammation. EPRAP was expressed on astrocytes and microglia in the brain. Deletion of EPRAP in mice resulted in the reduction of microglial accumulation and activation after systemic lipopolysaccharide injection. In addition, neuronal cell death was attenuated in kainic acid—induced hippocampal lesions. In vitro, EPRAP promoted microglial inflammation, which was mediated by mitogen-activated protein kinase kinase 4. EPRAP is a potential therapeutic target as it may worsen brain inflammation—mediated neuronal damage.

Modeling Mutant Bag3—Linked Cardiomyopathy

The missense mutation P209L in the Bcl2-associated anthanogene (BAG) 3 results in skeletal muscle and cardiac complications. To investigate its utility in modeling human disease, Quintana et al (Am J Pathol 2016, 186:1989–2007) generated cardiomyocyte-specific $\beta$MHC-human BAG3 P209L transgenic mice and characterized the progressive cardiac phenotype. At one year of age, mice underwent progressive heart failure and displayed preamyloid oligomers and related alterations. Surprisingly, increased numbers of activated cardiac fibroblasts were identified in Bag3 P209L transgenic mouse hearts without increased fibrosis. These findings point to a previously undescribed therapeutic target for mutation- and misfolded protein—associated cardiac disorders.

$\beta_2$ Integrins Promote Macrophage Fusion

The functions of the most abundant $\beta_2$ integrin $\alpha_{5}\beta_2$ (Mac-1) and the related integrin $\alpha_3\beta_2$ remain unclear in macrophage fusion, a hallmark of chronic inflammation. Using macrophages isolated from mice with deleted Mac-1 (Itgb2) and $\alpha_3\beta_2$ (Itgad) genes, Podolnikova et al (Am J Pathol 2016, 186:2105–2116) examined the formation of multinucleated giant cells (MGCs). During the resolution phase of inflammation, MGCs were formed in the inflamed mouse peritoneum and their numbers were approximately twofold higher in wild-type than in Mac-1—null mice. Both $\beta_2$ integrins supported macrophage fusion, and their contributions correlated with their relative abundance on the surface of macrophages. However, the counter-receptor ICAM-1 was not absolutely required for fusion. Mac-1 and $\alpha_3\beta_2$ support macrophage fusion, and future examinations should identify other proteins involved.

Estrogen Promotes Vasculogenesis in Endometriosis

Estrogen stimulates the growth of endometriotic lesions, which are further vascularized by the incorporation of endothelial progenitor cells (EPCs) into microvessels. Using an irradiated mouse model, Rudzitis-Auth et al (Am J Pathol 2016, 186:2129–2142) analyzed whether this vascularization is estrogen dependent. In vitro, estrogen-treated EPCs exhibited a higher migratory and tube-forming capacity than controls. When endometriotic lesions were surgically induced in vivo, estrogen stimulation improved early lesion microvasculature by incorporating significantly higher number of EPCs. Estrogen further stimulated the growth of lesions, which exhibited massively dilated glands with a flattened layer of stroma, mainly due to an increased glandular secretory activity. Targeting this hormonally-regulated vasculogenesis mechanism may allow development of future therapeutic approaches.

Targeting Lung Cancer with BMTP-11