This Month in AJP

Exploring Mast Cell Degranulation in the Eye

The role of mast cell degranulation in ocular pathology remains unresolved. To study this role, Bousquet et al (Am J Pathol 2015, 185:2083—2095) locally administered 48/80—a synthetic compound that releases histamine from mast cells—into rat eyes. Local mast cell degranulation provoked acute ocular inflammation and dilation and resulted in serous retinal detachment, a common clinical feature of retinal diseases. The levels of inflammatory mediators like tumor necrosis factor-\(\alpha\), chemokine (C-X-C motif) ligand 1, chemokine ligand 2, and IL-5, -6, -18, and -1\(\beta\) increased significantly in experimental eyes compared to control eyes. Preventing mast cell degranulation by inhibiting the release of inflammatory mediators may aid in managing chronic ocular diseases as well as acute ocular inflammation.

Linking Podocyte Injury and Foam Cell Infiltration

The progressive kidney disease focal segmental glomerulosclerosis (FSGS) is caused by podocyte injury. Using transgenic mouse models for FSGS, Hara et al (Am J Pathol 2015, 185:2118—2131) studied the link between podocyte injury and macrophage and foam cell infiltration. Although acute podocyte injury or severe hypercholesterolemia alone was insufficient for infiltration, combining drug-induced chronic podocyte injury with hypercholesterolemia promoted macrophage—derived foam cell infiltration via lipid peroxidation. This combination also resulted in glomerular lipid deposition, podocyte loss, and renal dysfunction as well as aberrant lysophosphatidylcholine (LPC) 16:0 and 18:0 formation. In vitro, LPC 16:0 and 18:0 accelerated glomerular macrophage—derived foam cell infiltration by mediating the expression of adhesion molecules and chemokines in resident cells. In human FSGS, glomerular macrophage—derived foam cells contained oxidized phospholipids along with the expression of chemokines in the tuft. Glomerular lipid modification represents a novel pathology by podocyte injury, promoting FSGS.

Understanding TGF-\(\beta\)—Induced Renal Fibrosis

Transforming growth factor (TGF)-\(\beta\) promotes tubulointerstitial fibrosis, a key pathological feature of progressive renal disease that results in loss of renal function. Thakur et al (Am J Pathol 2015, 185:2168—2180) studied the mechanism behind TGF-\(\beta\)—induced profibrotic signaling. TGF-\(\beta\) exerted its profibrotic action in vitro and in vivo via inactivation of adenosine monophosphate-activated protein kinase (AMPK). Consistently, AMPK activation markedly attenuated TGF-\(\beta\)1 functions whereas its inhibition enhanced basal as well as TGF-\(\beta\)1—induced phenotypic changes. Tuberin contributed to the protective effects of AMPK. TGF-\(\beta\)1 promoted cell injury by blocking AMPK-mediated tuberin phosphorylation and activation. In vivo, the significant decrease in AMPK phosphorylation as well as in tuberin phosphorylation on its AMPK-dependent activating site was associated with epithelial–mesenchymal transition. AMPK and tuberin activators may prove useful in preventing TGF-\(\beta\)—induced kidney fibrosis and progressive renal disease.

Modeling Neurocysticercosis

Lack of proper animal models impedes research on neurocysticercosis (NCC), infection of the central nervous system by the tapeworm Taenia solium. Verastegui et al (Am J Pathol 2015, 185:2259—2268) therefore generated a rat NCC model using intracranial infection with activated T. solium oncospheres. Infected rats developed cysticerci (cysts harboring larvae) in the parenchymal, ventricular, or submeningeal brain tissue after four months. The development of cysticerci was independent of the tested route of infection and the infectious dose, but the success of the infection depended on the age of the rat. The tissue surrounding the cysts showed specific features observed in human and porcine NCC. Nine percent of rats with NCC developed epilepsy. This novel rat NCC model is suitable to study human NCC.

Endometriosis Is Estrogen Dependent

The mechanisms behind endometriosis-associated pain remain unresolved; however, estrogen-dependent neuroinflammation has been implicated. Using in vivo and in vitro models, Greaves et al (Am J Pathol 2015, 185:2286—2297) studied the role of estradiol (E2) in the interaction between macrophages and nerve fibers in peritoneal endometriosis. Macrophages and nerve fibers were found in close association in peritoneal endometriosis lesions from women and mice; estrogen receptor \(\beta\) was the predominant estrogen receptor in these macrophages. In mice, E2 treatment increased macrophage infiltration of endometriosis lesions. In vitro, E2 promoted macrophage recruitment by nerve fibers, macrophage-targeting chemokine production by neuronal cells, and nerve fiber growth via neurotrophin synthesis by macrophages. Endometriosis is an estrogen-dependent neuroinflammatory disorder in which E2 mediates macrophage—nerve cross talk.