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This Month in *AJP*

Stromal Caveolin-1 Predicts Breast Cancer Prognosis

Caveolin-1 plays a major role in breast cancer tumorigenesis; however, the value of epithelial caveolin-1 as a prognostic marker has been limited. Witkiewicz et al (**Am J Pathol 174:2023–2034**) and Sloan et al (**Am J Pathol 174: 2035–2043**) therefore examined caveolin-1 expression in the stromal microenvironment of human breast cancer. Stromal expression of caveolin-1 correlated with reduced levels of metastasis, and caveolin-1 was not expressed in stroma of patients with poor clinical outcome. In addition, tumor onset in mice was accelerated in the absence of stromal caveolin-1. Caveolin-1 may therefore function as a tumor suppressor in the stromal microenvironment and serve as a new prognostic marker for breast cancer progression. These data are further highlighted in the accompanying Commentary (**Am J Pathol 174: 1996–1999**).

Novel Markers for Kidney Disease Progression

Only a minority of patients with chronic kidney disease progress to end-stage renal disease. Current clinical markers are not sufficient to reliably predict chronic kidney disease progression, which impedes targeted treatment of high-risk patients. Using the heterogeneous TGF-β1 transgenic mouse model of renal disease progression, Ju et al (**Am J Pathol 174:2073–2085**) applied transcriptional profiling to identify genes whose expression correlated with renal disease severity. They found that human orthologs of a subset of these candidates were associated with disease progression and glomerular filtration rate in human patients. These genes may therefore serve as novel markers for chronic kidney disease progression.

Urokinase Plasminogen Activator Receptor in Hyperoxia-Induced Lung Injury

Prolonged administration of high levels of supplemental oxygen, hyperoxia, can often effectively treat patients with respiratory failure. Hyperoxia, however, can induce or exacerbate lung injury in a process mediated by neutrophil infiltration. Van Zoelen et al (**Am J Pathol 174: 2182–2189**) hypothesized that urokinase plasminogen activator receptor (uPAR), which is important for leukocyte migration, plays a role in hyperoxia-induced lung injury. They found increased levels uPAR-expressing neutrophils in lungs of hyperoxia-treated mice, as compared with control mice. In addition, both neutrophil infiltration and lung injury were reduced in hyperoxia-treated uPAR-deficient mice. Thus, inhibiting uPAR may ameliorate lung injury during therapeutic oxygen administration.

Immunoregulation in Tuberculosis Lesions

Although the Th1 immune response is critical for fighting *Mycobacterium tuberculosis* (Mtb) infection, cell-mediated immune responses rarely eradicate Mtb. Instead, Mtb-infected macrophages generate granulomas, which become sites of chronic inflammation. Rahman et al (**Am J Pathol 174: 2211–2224**) found low numbers of perforin- and granzyme-expressing $CD8^+$ T cells in granulomatous lesions in children with local tuberculosis lymphadenitis; however, these granulomas contained increased numbers of $FoxP3^+$ regulatory T cells. In addition, Mtb-infected lymph nodes expressed high levels of the immunoregulatory cytokine transforming growth factor-β but low levels of the pro-inflammatory cytokines interferon-γ, tumor necrosis factor-α, and interleukin-17. These data suggest that local immunoregulation may contribute to the establishment of Mtb infection.

Synthetic Retinoic Acid Ameliorates Autoimmunity

Th17 cells, $CD4^+$ T-helper cells that secrete IL-17, play a pathogenic role in autoimmune diseases such as multiple sclerosis. Using a mouse model of multiple sclerosis, experimental autoimmune encephalitits, Klemann et al (**Am J Pathol 174: 2234–2245**) found that AM80, a synthetic retinoid with improved biological function over *all trans* retinoic acid, inhibited Th17 cell differentiation and effector function *in vitro* and *in vivo*, without generating general immunosuppression. AM80 also suppressed IL-10 expression in a Th17-like subset of regulatory T cells. AM80 treatment was effective in inhibiting early experimental autoimmune encephalitits symptoms, even if administered after disease initiation, but it did not prevent chronic symptoms. Therefore, AM80 is a promising therapy for the treatment of multiple sclerosis and other Th17-mediated autoimmune diseases.

Phagocytosis without Disrupting the Blood-Retinal Barrier

Phagocytic cells remove damaged photoreceptors following retinal injury; however, the blood-retinal barrier is thought to prevent access of inflammatory cells into the

eye. To identify the source of the phagocytic cells that respond to retinal injury, Joly et al (**Am J Pathol 174: 2310–2323**) used a mouse model of light-induced photodamage with either fluorescently labeled bone marrow-derived cells or microglia. They found that both bone marrow- and microglia-derived macrophages were involved in the phagocytosis of dead photoreceptors. Bone marrow-derived macrophages focused on the site of the injury, whereas microglia were activated in the entire retina of the light-exposed eye. Bone marrow-derived macrophages migrated into the eye without damaging the blood-retinal barrier, and both bone marrow- and microglia-derived macrophages entered the circulation following photoreceptor phagocytosis. Macrophages laden with retinal antigen may then contribute to retinal autoimmunity following injury.