This Month in AJP

Modeling Castration-Resistant Prostate Cancer

In many men receiving androgen-deprivation therapy for prostate cancer, the disease progresses to castration-resistant prostate cancer (CRPC). To identify the key molecular events regulating castration-resistant growth, Knuuttila et al (Am J Pathol 2014, 184:2163–2173) established a pre-clinical mouse model of CRPC based on orthotopic vertebral cancer of prostate xenografts grown in castrated hosts. This model exhibited the key characteristics of clinical CRPC, including up-regulation of intratumoral androgen biosynthesis, aberrant androgen receptor expression, and responsiveness to androgen receptor antagonists. This pre-clinical model offers a valuable tool to identify and test novel anti-CRPC therapies.

Understanding Tissue Destruction in Bullous Pemphigoid

Existing neonatal mouse models for the autoimmune skin diseases bullous pemphigoid (BP) and epidermolysis bullosa acquisita implicate different Fcγ receptors (FcγRs). To better define the immune components involved in tissue destruction, Schulze et al (Am J Pathol 2014, 184:2185–2196) developed an adult mouse model of experimental BP. Tissue destruction was completely dependent on the Fc-portion of anti–collagen-17 immunoglobulin and was mediated by FcγRIV and, to a lesser extent, by FcγRIIa. FcγRIIB was protective whereas FcγRI was nonessential. Importantly, drug-induced inhibition of FcγRIV and depletion of granulocytes abolished skin blisters. This model enables exploration of mechanisms of autoantibody-mediated tissue destruction and novel treatment options in a mouse model with pre-existing skin lesions.

Age-Dependent Changes Influence Muscle Regeneration

The process of aging further complicates regenerative responses to injury, including that of muscle. Zhou et al (Am J Pathol 2014, 184:2225–2236) characterized tissue regeneration in young, adult, and aged rats after compartment syndrome injury. Significant differences were observed in the regeneration process of differently aged rats involving muscle function, tissue anatomy, myogenesis, neovascularization, and innervation. Compared to recovery in young rats, adult rats had delayed functional recovery, and aged rats were deficient in their regenerative capacity. Age-dependent changes in both the contractile apparatus restoration and myogenesis must be considered when designing therapies for muscle injury.

Smad2/3 Play Opposing Roles in Peritoneal Fibrosis

Patients receiving continuous ambulatory peritoneal dialysis (CAPD) risk peritoneal fibrosis, a major cause of ultrafiltration failure. Duan et al (Am J Pathol 2014, 184:2275–2284) examined TGF-β1/Smad signaling in peritoneal biopsies associated with CAPD and in a mouse model of peritoneal dialysis fluid–induced peritoneal fibrosis. TGF-β1/Smad2/3 signaling was highly activated in CAPD patients with increased collagen deposition and thickening of the peritoneal membrane. Smad3 deletion in mice prevented drug-induced peritoneal fibrosis whereas loss of Smad2 exacerbated both peritoneal fibrosis and dysfunction. Opposing roles for Smad2 and Smad3 were also observed in cultured mouse mesothelial cells. These findings provide a mechanistic basis for future therapies targeting TGF-β1/Smad signaling in peritoneal fibrosis.

Angiopoietins Promote Ovarian Cancer Growth

Angiopoietins (Angpts) may play an essential role in cancer progression, but their role in ovarian cancer remains largely unknown. Brunckhorst et al (Am J Pathol 2014, 184:2285–2296) examined the expression profile and biological effects of Angpts in ovarian cancer. Human ovarian cancer cells and tissues showed increased expression of ANGPT1, ANGPT2, and ANGPT4 as well as the Angpt receptor TIE2. In experimental mice increased Angpt1, Angpt2, or Angpt4 expression promoted i.p. ovarian cancer growth and shortened survival. Angpts promoted accumulation of cancer-associated fibroblasts (CAFs), stimulated tumor angiogenesis, enhanced ovarian cancer cell proliferation and invasion in vivo, and induced Tie-2 and Erk1/2 activation in ovarian CAFs. The Angpt–Tie-2 functional axis thus represents an attractive target for ovarian cancer therapy.