This Month in AJP

Exploring RASA1 Roles in Blood Vascular Disorder

In most patients, capillary malformation—arteriovenous malformation (CM-AVM) is attributed to inactivating mutations of RASA1 gene. To assess how RASA1 loss induces blood vascular (BV) abnormalities, Lubeck et al (Am J Pathol 2014, 184:3163–3169) generated a knockin mouse expressing a mutated form of RASA1 (R780Q) that specifically abrogates RASA1 catalytic activity. Homozygous RASA1 (R780Q)R780Q mice showed the same severe BV abnormalities as Rasa1-null mice and died midgestation. Dysregulated Ras pathway activation, not loss of a Ras-independent function of RASA1, resulted in BV abnormalities in CM-AVM. Ras signaling inhibition may provide an effective CM-AVM therapy.

Linking Prostatitis and Prostate Cancer

The link between prostatitis (prostate gland inflammation) and prostate cancer development remains unclear. Burcham et al (Am J Pathol 2014, 184:3176–3191) studied this link by inducing prostate-specific inflammation in a mouse prostate cancer model and tracking prostate size over time by bioluminescence. Acute prostatitis increased epithelium proliferation and prostate size. However, at four months prostatitis mice showed similar numbers of precancerous epithelial lesions and slightly decreased average grade of lesions compared with control mice. At later time points, mice with induced inflammation exhibited more carcinoma development. Analyzed as one cohort, prostatitis positively correlated with lesion number and grade. Specifically, myeloid-based inflammation correlated with lesion development. This model may further delineate the link between inflammation and prostate cancer development.

Macrophages Promote Fracture Healing

The specific macrophage subtypes associated with fracture repair phases during bone tissue formation remain unknown. Pairing murine models of femoral fracture and inducible macrophage depletions, Raggatt et al (Am J Pathol 2014, 184:3192–3204) explored contributions of macrophages in fracture healing. Inflammatory macrophages localized with initiating chondroinvasion centers, persisted within granulation tissue at the expanding soft callus front, and were associated with key events during soft-to-hard callus transition. Resident macrophages predominated in the maturing hard callus. Inflammatory macrophages were required for initiation of fracture repair, whereas both inflammatory and resident macrophages promoted anabolic mechanisms during endochondral callus formation. Various macrophages impart substantive and prolonged contributions to fracture healing, representing viable therapeutic targets for enhancing repair mechanisms.

FIH-1 Positively Regulates Keratinocyte Migration

The hydroxylase factor-inhibiting hypoxia-inducible factor-1 (FIH-1) affects several signaling pathways in keratinocytes, such as epidermal growth factor receptor (EGFR), which is known to promote migration and wound repair. Peng et al (Am J Pathol 2014, 184:3262–3271) investigated the functional significance of this pathway in mice and cell culture. FIH-1-null mice exhibited delayed wound healing. In cell culture, FIH-1 increased EGFR signaling, enhanced keratinocyte migration (via mitogen-activated protein kinase pathway), and activated extracellular signal-regulated kinase 1/2. Binding studies identified leucine-rich-repeat kinase 1 (LRRK1) as a partner of FIH-1. However, LRRK1–FIH1 binding abrogated EGFR/LRRK1 complex formation; further studies confirmed that FIH-1 regulates EGFR signaling by preventing EGFR turnover. The identification of LRRK1 as a substrate for FIH-1 opens new avenues to explore epithelial migration, especially in wound healing.

Cancer Cell Conditioning of Macrophages by uPAR

The urokinase-type plasminogen activator receptor (uPAR) promotes cancer cell survival, proliferation, and metastasis. Hu et al (Am J Pathol 2014, 184:3384–3393) examined the specific role of uPAR in inflammatory cell conditioning in the tumor microenvironment. uPAR expression in diverse cancer cell types promoted their ability to polarize co-cultured macrophages toward an M2 (tumor-associated macrophage) phenotype. uPAR-expressing cancer cells also stimulated expression of transforming growth factor β (directly via uPA) and interleukin-4 (via activated ERK1/2). Further exploring cancer-cell uPAR in specific cancers will help elucidate molecular mechanisms that can be targeted for therapy.