

This Month in *AJP*

CAR Drives to Sites of Pulmonary Hypertension

Pulmonary arterial hypertension (PAH), defined by elevated pulmonary vascular resistance, eventually leads to right heart failure and premature death. To combat a lack of selective targeted therapy, Urakami et al (*Am J Pathol* 2011, 178:2489–2495) investigated the cyclic peptide CARSKNKDC (CAR). When intravenously administered to PAH rats, CAR accumulated in experimentally induced hypertensive lungs but not in healthy tissue. CAR homed to all layers of remodeled pulmonary arteries and to capillary vessels and interstitial space of the PAH lungs, suggesting the clinical utility of CAR in the targeted delivery of therapeutic compounds to PAH lungs.

Edema Toxin and Anthrax—Seeing Is Believing

Noninvasive imaging techniques enable real-time tracking of pathogen-host interactions *in vivo*. Dumetz et al (*Am J Pathol* 2011, 178:2523–2535) visualized wild-type *Bacillus anthracis* in guinea pig and mouse hosts by using bioluminescence imaging coupled with histology. Edema toxin (ET), but not lethal toxin (LT), markedly modified the patterns of bacterial dissemination, with direct dissemination to the spleen and apoptosis of lymphoid cells. When produced together during infection, early lesions were typical of LT, whereas later lesions, of ET. These data propose a greater role than previously suspected for ET in anthrax, suggesting that therapeutic targeting of ET may contribute to protection.

Adiponectin and PPAR γ in Stellate Cell Activation

Altered hepatic pathology, function, or both are common sequelae of the metabolic syndrome. Shafiei et al (*Am J Pathol* 2011, 178:2690–2699) asked how adiponectin modulates hepatic stellate cell activation and fibrogenesis using transgenic mouse models. Mice overexpressing adiponectin were resistant to experimental fibrosis whereas adiponectin-null animals developed severe fibrosis. In wild-type stellate cells overexpressing adiponectin, mRNA expression of PPAR γ , SREBP1c, and

CEBP α was significantly increased. The PPAR γ agonist troglitazone prevented upregulation of collagen α 1(I) and α -SMA mRNA in wild-type stellate cells but had no effect on adiponectin-null stellate cells. These findings elucidate the complicated relationship between PPAR γ and adiponectin in stellate cell activation.

Restoring Immune Responses in Ataxia-Telangiectasia

Ataxia-telangiectasia (A-T) patients and mice that lack the protein kinase ATM exhibit immune system-related pathology. Using the lymphocytic choriomeningitis virus (LCMV) model, D'Souza et al (*Am J Pathol* 2011, 178:2740–2751) found that *ATM*^{-/-} mice, despite having fewer naïve CD8⁺ T cells, effectively cleared the virus. They observed aberrant CD8⁺ T-cell responses, including defective expansion and contraction, effector-to-memory differentiation, and a switch in viral-epitope immunodominance. Inhibition of Akt or mTORC1 during T-cell receptor activation alone rescued the proliferation defect, and rapamycin treatment of *ATM*^{-/-} mice during LCMV infection increased the number of memory T cells. Targeting Akt and/or mTORC1 may thus be of therapeutic value in restoring immune responses in A-T patients.

HNSCC Invasion Proceeds without Macrophages

Invasion of tumor cells into the local stroma is an important component in cancer progression. Smirnova et al (*Am J Pathol* 2011, 178:2857–2865) examined *in vivo* invasion of HNSCC cells in response to applied gradients of epidermal growth factor (EGF) and the chemokine CXCL12. Invading cells were >75% tumor cells, about 15% macrophages, and <10% unidentified cells. Although macrophages were present, they were not required for HNSCC invasion. CXCL12-induced *in vivo* invasion of HNSCC cells occurred via a unidirectional transactivation of EGFR through CXCR4. CXCL12 activation of EGFR appeared to occur via release of EGFR ligands. Thus, these data support treatment of HNSCC with EGFR inhibitors to inhibit local invasion independent of effects on tumor growth rate.