This Month in AJP

CAR Selectively Enhances Drug Efficacy in PAH

A major limitation in the treatment of pulmonary arterial hypertension (PAH) is the lack of pulmonary vascular selectivity. Toba et al (Am J Pathol 2014, 184:369–375) tested the effect of co-administration of CARSKNKDC (CAR), which specifically targets PAH vasculature, on three vasodilators in hypoxia/normoxia-exposed PAH rats. Intravenously co-administered CAR enhanced pulmonary but not systemic effects of the vasodilators farsudil and imatinib in PAH rats. CAR increased lung tissue imatinib concentration in isolated PAH lungs without increasing pulmonary vascular permeability. Sublingual CAR was also effective in selectively enhancing the pulmonary vasodilation by imatinib and sildenafil. These results suggest a new paradigm for target tissue-specific pharmacological intervention in PAH.

Micro-CT Uncovers Tumor Micromorphology and Vascularization

Using four tumor models characterized by different degrees of aggressiveness and angiogenesis, Ehling et al (Am J Pathol 2014, 184:431–441) tested the ability of X-ray micro-computed tomography (μCT) to yield accurate blood volume (rBV) quantification. rBV values obtained via in vivo μCT ranged from 2.6% to 6.0%, similar to IHC values. Ultra-high-resolution ex vivo μCT enabled visualization of blood vessels as small as 3.4 mm and vessel branches up to the seventh order. Vessel size and vessel branching correlated very well with tumor aggressiveness and angiogenesis. Thus, combining highly accurate functional with highly detailed anatomical μCT represents a useful tool for facilitating high-throughput quantitative and translational angiogenesis research.

Diuretics Prevent Thiazolidinedione-Induced Cardiac Hypertrophy

Thiazolidinedione (TZD)-induced cardiac hypertrophy (CH) has been attributed to an increase in plasma volume or a change in cardiac nutrient preference. To test the hypothesis that TZD-induced CH is directly mediated through volume expansion, Chang et al (Am J Pathol 2014, 184:442–453) released TZD-induced volume overload by feeding mice diuretics and examined PPARγ dependence by using PPARγ heterozygous knockout (Pparg+/−) mice and mice defective for ligand binding (Pparg+/-/+). Rosiglitazone-induced CH in mice was mediated through PPARY activation and required intact ligand binding. Diuretics attenuated rosiglitazone-induced CH, hypertrophic gene reprogramming, cardiomyocyte apoptosis, hypertrophy-related signal activation, and left ventricular dysfunction. Such a successful cotreatment strategy could be easily adopted in a clinic.

α7 nAChR Agonist Enhances Cognition

Enhancing cholinergic signaling with acetylcholinesterase inhibitors remains the primary strategy for improving cognition in Alzheimer disease (AD), though the benefits are typically short-lived. Medeiros et al (Am J Pathol 2014, 184:520–529) examined the effect of long-term treatment with a selective α7 nicotinic acetylcholine receptor (nAChR) agonist (A-582941) in aged 3xTg-AD mice with robust AD-like pathology. Overall, pathological findings (β-amyloid deposits, tau phosphorylation, and neuroinflammation) were unchanged. However, cognition was completely restored in aged 3xTg-AD mice to the level of that in age-matched nontransgenic mice and was accompanied by activation of transcriptional factors c-Fos and CREB, up-regulation in BDNF levels, and phosphorylation of the TrkB receptor. Activating α7 nAChR may be a promising treatment for cognitive impairment in AD.

Cervical Cancer Recurrence after Raloxifene Treatment

The selective estrogen receptor modulator (SERM) raloxifene promotes regression of high-grade dysplasia and cancer arising in the cervix of K14E6/E7 transgenic mice treated chronically with estrogen. Spurgeon et al (Am J Pathol 2014, 184:530–540) evaluated the recurrence of cervical cancer following raloxifene therapy in these mice. Neoplastic disease recurred following cessation of raloxifene treatment regardless of exogenous estrogen, though it did increase the severity of the recurrent neoplastic disease. All recurrent cancers retained an active estrogen/ERα signaling pathway and were responsive to treatment with raloxifene, and maintaining mice on raloxifene prevented high recurrence rates. This study supports the premise that SERMs may be effective in treating HPV-associated human cervical cancers, but their effectiveness may require long-term treatment.