This Month in AJP

Identifying Medullary Thyroid Carcinoma Biomarkers

There exists a genotype-phenotype correlation with specific germ line RET mutations in medullary thyroid carcinoma (MTC), but the pathways involved remain unknown. Maliszewska et al (Am J Pathol 2013, 182:350–362) used transcriptional profiling to identify signaling pathways and specific biomarkers related to familial (PROM1, LOXL2, GFRA1, and DKK4 associated with RETM918T) and sporadic MTC (GAL associated with RET634). Genes associated with MTCM918T were mainly involved in proliferative, cell adhesion, and general malignant metastatic effects, as well as Wnt, Notch, NFκB, JAK/Stat, and MAP kinase signaling pathways. Silencing PROM1 via siRNA cells harboring RETM918T caused an increase in apoptotic nuclei, suggesting that PROM1 is necessary for the survival of these cells. These data identify new therapeutic targets to improve MTC management.

miR-199a-5p Regulates Urothelial Permeability in Bladder Pain Syndrome

Defects in urothelial integrity resulting in leakage and activation of underlying sensory nerves are potential causative factors of bladder pain syndrome, a clinical syndrome of idiopathic pelvic pain and urinary urgency/frequency. Monastyrskaya et al (Am J Pathol 2013, 182:431–448) identified miR-199a-5p as an important regulator of intercellular integrity. Upon overexpression in urothelial and bronchial epithelial cells, miR-199a-5p impaired tight junction formation and led to increased epithelial permeability. miR-199a-5p directly targeted mRNAs encoding LIN7C, ARHGAP12, PALS1, RND1, and PVRL1 and attenuated their expression levels to a similar extent. The data demonstrate for the first time that miRNA expression influences urothelial permeability and might underlie the changes in bladder urothelium observed in bladder pain syndrome.

PPARγ in Prostate Differentiation

Stromal-epithelial interactions are crucial for the development of hind gut-derived endoderm into rectal, prostatic, and bladder phenotypes; however, the precise mechanisms by which epithelium responds to stromal cues remain unknown. Strand et al (Am J Pathol 2013, 182:449–459) examined the role of proliferator activated receptor gamma (PPARγ) isoforms and PTEN activity in prostate differentiation. Knockdown experiments demonstrated that PPARγ2 is essential for urothelial transdifferentiation. Knockdown of both PPARγ isoforms 1 and 2 arrested urothelial differentiation of benign human prostate epithelial (BHPRE) cells. Although PTEN deficiency alone induced latent squamous differentiation in BHPRE cells, combined PPARγ and PTEN deficiency accelerated the development of keratinizing squamous metaplasia. These data suggest a role for the regulation of epithelial cellular metabolism in the process of differentiation.

Tamoxifen Ameliorates Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is characterized by progressive muscle wasting, respiratory and cardiac impairments, and premature death. Using the mdx5C mouse model of DMD, Dorchies et al (Am J Pathol 2013, 182:485–504) identified tamoxifen—used to treat estrogen-dependent breast cancer—as helpful in DMD therapy. Oral tamoxifen treatment stabilized myofiber membranes, normalized whole body force, and increased force production and resistance to repeated contractions of the triceps muscle. Tamoxifen also improved the structure of leg muscles, diminished cardiac fibrosis, and reduced diaphragm fibrosis, while increasing its thickness, myofiber count, and myofiber diameter and conferred a markedly slower phenotype to the muscles. Interestingly, estrogen receptors (ERs) α and β were significantly increased in dystrophic compared to normal muscles, and tamoxifen normalized the relative abundance of ERβ isoforms. These findings suggest that tamoxifen might be a useful therapy for DMD.

Optimizing Macrophages for Muscle Regrowth

Growing evidence suggests that macrophages possess major myogenic capacities. Dumont et al (Am J Pathol 2013, 182:505–515) used in vivo and in vitro atrophy models to investigate the impact of stimulating macrophages with...
macrophage-colony stimulating factor (M-CSF) on muscle regrowth. M-CSF significantly increased the total macrophage density in soleus muscle and promoted a wound-healing macrophage phenotype, better and faster muscle fiber diameter, and function recovery. In vitro co-culture of myotubes and macrophages confirmed that the M-CSF-induced switch in macrophage phenotype promoted myotube growth by decreasing protein degradation. This study establishes that macrophage myogenic capacities can be modulated to optimize muscle recovery and regrowth.