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This Month in *AJP*

Biomarkers Found for Human Metaplasia and Gastric Cancer

Early diagnosis and curative resection are associated with increased survival in gastric cancer patients. Yet, a majority of gastric cancers are still diagnosed at later stages. Sousa et al (**Am J Pathol 2012, 181:1560–1572**) uncovered novel biomarkers LTF and DNMT1 for spasmolytic polypeptide-expressing metaplasia and intestinal metaplasia, respectively, by generating proteome profiles using formalin-fixed, paraffin-embedded samples of interstitial-type gastric cancer, metaplasia, and normal mucosa by combining peptide isoelectric focusing and liquid chromatography-mass spectrometry/mass-spectrometry analysis. The authors further established that the loss of LTF or DMBT1 expression in gastric tumors correlates with a poor prognosis.

Large Oncosomes and Aggressiveness in Prostate Cancer

Oncosomes are tumor-derived microvesicles that transmit signaling complexes between cell and tissue compartments. Di Vizio et al (**Am J Pathol 2012, 181: 1573–1584**) demonstrated that such oncosomes contain metalloproteinases, RNA, caveolin-1, and the GTPase ADP-ribosylation factor 6 and are biologically active toward tumor cells, endothelial cells, and fibroblasts. Flow cytometry-based methods can selectively sort and analyze large oncosomes in mouse prostate cancer models and human tumor tissues, demonstrating a correlation with tumor progression in mice. Aside from establishing techniques for the visualization, isolation, quantification, and characterization of large tumor vesicles in tissues and in the circulation, these findings suggest a mechanism of conditioning tumor microenvironment and distant site by migrating tumor cells, thereby potentiating advanced disease.

Necrostatin-1 Therapy for Retinal Detachment

Necroptosis, or programmed necrosis, is important in embryonic development and pathophysiology as well as neuronal cell death. Dong et al (**Am J Pathol 2012, 181: 1634–1641**) investigated the role of the necroptosis inhibitor necrostatin-1 on photoreceptor survival and functional experimental retinal detachment in rats. By introducing necrostatin-1 into the subretinal space at the time of retinal detachment and 6 hours later, they observed that necrostatin-1 directly protected neurons by specifically inhibiting necroptotic cell death, inhibited receptor interacting protein kinase phosphorylation induction after retinal detachment, attenuated retinal degeneration, preserved retinal thickness, rescued neurons in the outer retinal layers, and reduced functional impairment after retinal detachment. There is therefore a promising therapeutic role for necrostatin-1 in protecting photoreceptors from necroptosis and improving functional outcome.

TIMP-3 Predicts Survival and Relapse in Non–Small Cell Lung Cancer

Tissue inhibitor of metalloproteinase-3 (TIMP-3) is essential for limiting inflammation. Wu et al (**Am J Pathol 2012, 181: 1796–1806**) hypothesized that TIMP-3 loss would induce chronic inflammation, promoting tumor malignancy in human papillomavirus (HPV)-infected non–small cell lung cancer. TIMP-3 loss was more frequent in HPV 16/18-positive tumors than in E6-negative tumors. Promoter hypermethylation resulted in decreased TIMP-3 expression, leading to cell invasion and anchorage-independent growth due to increased IL-6 production in otherwise E6-negative TL4 and CL-10 lung cancer cells expressing E6. Patients with low-TIMP-3/high-IL-6 tumors had shorter overall survival and relapse-free survival periods than patients with high-TIMP-3/low-IL-6 tumors. TIMP-3 may serve as a prognostic marker for tumor recurrence in patients after surgical resection, and its loss may promote tumor malignancy, subsequent relapse, and poor survival in patients with HPV-infected non–small cell lung cancer.

miR-200c Inhibits Melanoma Progression

The role of miRNAs in melanoma progression and drug resistance has not been well studied. Liu et al (**Am J Pathol 2012, 181:1823–1835**) analyzed the role of miR-200c in melanoma progression and demonstrated that miR-200c is down-regulated in melanomas compared with melanocytic nevi. miR-200c overexpresion in melanoma cells resulted in decreased cell proliferation, migratory capacity, and drug resistance that could be rescued by *Bmi-1* overexpression; down-regulation of BMI-1, ABCG2, ABCG5, and MDR1 with a concomitant increase in E-cadherin levels and *in vivo* inhibition of melanoma xenograft growth and metastasis with decreased BMI-1 expression and E-cadherin levels in tumors were also observed. Thus, miR-200c represents a critical target for increasing melanoma sensitivity to clinical therapies.