The American Journal of Pathology, Vol. 180, No. 6, June 2012

http://dx.doi.org/10.1016/j.ajpath.2012.04.002

This Month in *AJP*

Improving Prediction of Relapse in Prostate Cancer

Predicting the clinical outcome of prostate cancer remains a major challenge, even with prostate-specific antigen (PSA) monitoring. Using specific copy number variation (CNV) patterns in tumor or benign prostate tissues adjacent to cancer samples, Yu et al (Am J Pathol 2012, 180:2240–2248) generated prediction models of prostate cancer relapse or short PSA doubling time (PSADT). In addition, mean and median sizes of CNV from patients' blood, benign prostate tissues adjacent to the tumor, and tumor samples were also predictive of these clinical outcomes, independent of specific genes and regions. By using median-sized CNV from blood and tumor, the genome model correctly predicted cases for both relapse and short PSADT. Thus, CNV genome analysis of blood, normal prostate, or tumor tissues of prostate cancer patients holds promise for more efficiently and accurately predicting the behavior of prostate cancer.

New Roles for p53 in Mitochondrial Homeostasis and Antiretroviral Toxicity

The direct roles of p53 in mitochondrial DNA (mtDNA) replication and function are not well understood. Koczor et al (Am J Pathol 2012, 180:2276–2283) used a mitochondrial-targeted p53 (MTS-p53) to tease out p53's effects. MTS-p53 decreased cellular proliferation and mtDNA abundance in HepG2 cells transfected with wild-type human p53. Treatment of MTS-p53 cells with nucleoside reverse transcriptase inhibitor (NRTI) led to mtDNA depletion. A truncated p53 (MTS-p53-290) that localizes exclusively to the mitochondria caused cells to proliferate at control levels but yielded decreased mtDNA abundance and mitochondrial function following NRTI treatment. Further, the MTS-p53-290 cells demonstrated that only the nuclear fraction of p53 controlled cellular proliferation. This work demonstrates that overexpression of p53 negatively affects the normal mitochondrial homeostasis in the cells, thus providing new insights into p53's roles in the cell.

NS1 Single Point Mutation (Y89F) Limits Influenza A Virus Virulence

The nonstructural protein 1 (A/NS1) of influenza A viruses (IAVs) harbors several Src homology (SH)-binding motifs (bm) that mediate interactions with cellular proteins. The highly conserved Y89 of SH2bm prompted Hrincius et al (Am J Pathol 2012, 180:2361–2374) to evaluate its necessity for IAV virulence. The highly conserved SH2bm was crucial for efficient replication of IAV *in vitro* and *in vivo*. Furthermore, in an *in vivo* mouse model, disruption of this motif (Y89F) restricted virus distribution in the entire mouse lung, limited replication almost entirely to the alveoli, reduced the inflammatory response and pathological changes in the lung, and resulted in dramatically reduced virulence. These findings demonstrate that the change of a single residue of the highly conserved SH2bm within the A/NS1 restricts virus spread and strongly reduces virulence, further fostering A/NS1 as suitable target for antiviral interventions.

CTGF *Causes Glaucoma by Modifying the Trabecular Meshwork*

The most critical risk factor for optic nerve damage in primary open-angle glaucoma (POAG) is increased intraocular pressure (IOP) caused by a resistance to aqueous humor outflow in the trabecular meshwork (TM). The TGF-β2 target gene connective tissue growth factor (*CTGF*) is highly expressed in the TM. Junglas et al (Am J Pathol 2012, 180:2386–2403) demonstrate that increased expression of CTGF in mice causes phenotypes similar to that observed in patients with POAG: open iridocorneal angle, high IOP, and degeneration of optic nerve axons. The mechanism for increased IOP in mice appears to involve direct action of CTGF on the TM actin cytoskeleton, a scenario that might be similarly involved in the pathogenesis of POAG. The CTGF-overexpressing mice therefore provide a model that mimics human POAG and offers a molecular mechanism to explain the increase of its most critical risk factor.

MacroH2A1.1 Expression Can Predict Outcome in Colon Cancer

Histone variant macroH2A1 has two splice isoforms, macroH2A1.1 and macroH2A1.2, that possess tissue- and cell-specific expression patterns, with studies in breast and lung cancer demonstrating a strong correlation between macroH2A1.1 levels and proliferation. Sporn and Jung (Am J Pathol 2012, 180:2516–2526) assessed the differential regulation and predictive potential of macroH2A1 isoforms in colon cancer. MacroH2A1.1 mRNA was down-regulated in primary colorectal cancer samples compared to matched normal colon tissue, whereas macroH2A1.2 was up-regulated. At the protein level, macroH2A1.1 down-regulation correlated significantly with patient outcome, and loss with a worse outcome. Loss of macroH2A1.1 *in vitro* was associated with cell growth and metastasis. These data demonstrate the differential regulation of macroH2A1 isoforms in colon cancer, thus identifying macroH2A1.1 as a novel colon cancer biomarker.