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This Month in *AJP*

A Methyl Deviation Index for Breast Cancer

DNA methylation analysis provides a promising avenue for identifying distinct breast cancer phenotypes using candidate gene measurements and microarray analyses. Killian et al (**Am J Pathol 2011, 179:55–65**) performed a large-scale DNA methylation analysis of breast cancers and benign parenchyma. A methyl deviation index (MDI) was calculated for each lesion relative to terminal ductal-lobular unit baseline. Group comparisons revealed that high-grade and short-survival estrogen receptor–positive (ER^+) cancers had a significantly higher MDI than low-grade and long-survival ER^+ cancers whereas ER^- cancers had a significantly lower MDI. MDI showed superior prognostic performance to crude methylation levels, retaining prognostic significance in Cox multivariate analysis. Overall, MDI can be readily measured from routine breast pathology samples, correlates with aggressive cancer features, and is informative to estimate disease prognosis for ER+ primary invasive carcinomas.

Serum Enzymes Increase with Kupffer Cell Reduction

Macrophage colony-stimulating factor (M-CSF) directs differentiation of monocytes into Kupffer cells (KCs), which remove excess serum enzymes that are present following liver or muscle injury. Using three different animal models, Radi et al (**Am J Pathol 2011, 179:240–247**) asked whether increases in serum enzymes result from decreases in KCs in the apparent absence of hepatic or muscle injury. Antibody-mediated neutralization of M-CSF activity reduced the $CD14^+CD16^+$ monocyte population, depleted KCs, and increased serum enzyme levels in cynomolgus macaques. When rats were treated with clodronate liposomes, KCs were depleted and serum enzyme levels increased, again without evidence of tissue injury. Finally, in osteopetrotic ($Csf1^{op}/Csf1^{op}$) mice lacking functional M-CSF and having reduced levels of KCs, the levels of serum enzymes were higher than in wild-type littermates. Thus, depletion of KCs is associated with increased levels of short-lived serum enzymes, even in the absence of liver or muscle injury.

IL-17 Induces Pulmonary Pathogenesis during RSV Infection

Severe respiratory syncytial virus (RSV) infections cause airway damage, mucus hypersecretion, and Th2 cytokine production. Mukherjee et al (**Am J Pathol 2011, 179:248–258**) observed IL-17 levels in samples from severely ill infants with RSV infection and in a mouse model of RSV infection. In mice, neutralization of IL-17 during infection significantly reduced mucus production, inflammation, and viral load and significantly increased RSV-specific $CD8^+$ T cells. T-bet, IFN-γ, eomesodermin, and granzyme B were significantly up-regulated after IL-17 blockade, and *in vitro* analyses suggest that IL-17 directly inhibits T-bet, eomesodermin, and IFN-γ in $CD8^+$ T cells. In RSV-induced exacerbation of allergic airway responses, IL-17 neutralization significant decreased the exacerbated disease, reducing mucus production and Th2 cytokines levels as well as viral protein production. Together, these data reveal a pathogenic role for IL-17 in RSV-induced disease.

Stem Cells in This Old Heart of Mine

It is unknown whether defects in stem cell growth and differentiation contribute to myocardial aging and chronic heart failure (CHF) and whether a compartment of functional human cardiac stem cells (hCSCs) persists in the decompensated heart. Cesselli et al (**Am J Pathol 2011, 179:349–366**) address these questions by evaluating the properties of hCSCs in control and explanted hearts. Chronological age was a major predictor of five biomarkers of hCSC senescence: telomeric shortening, attenuated telomerase activity, telomere dysfunction-induced foci, and $p21^{Cip1}$ and $p16^{INK4a}$ expression. CHF had similar consequences for hCSCs, suggesting that defects in the balance between cardiomyocyte mass and the pool of nonsenescent hCSCs may condition the evolution of the disease. These results demonstrate that telomere dysfunction in hCSCs is a biomarker of aging and heart failure.

Modeling Colon Adenocarcinomas in 3D

Normal fibroblasts and cancer-associated fibroblasts (CAFs) display distinct gene expression signatures that may influence tumor cell migration, proliferation, and survival during tumor progression. To test this hypothesis, Dolznig et al (**Am J Pathol 2011, 179:487–501**) established a three-dimensional (3D) cell culture system using human colon tumor cells grown as multicellular spheroids that were subsequently co-cultured with normal fibroblasts or CAFs in collagen I gels. In this model, genes involved in invasion, extracellular matrix remodeling, inflammation, and angiogenesis were differentially regulated. The modular setup, reproducibility, and robustness of the system allow identification of target molecules involved in signaling pathways that mediate paracrine interactions in the tumor microenvironment as well as validation of such targets during tumor growth and invasion in the supporting stroma.