The American Journal of Pathology, Vol. 174, No. 3, March 2009

DOI: 10.2353/ajpath.2009.081137

This Month in *AJP*

Effects of Highly Active Antiretroviral Therapy (HAART) on Pulmonary Arteries

HAART consists of at least three antiretroviral drugs that suppress viral replication and restore $CD4^+$ T-cell numbers in HIV-infected patients. HAART dramatically improves the prognosis of HIV-infected patients; however, HAART drugs may increase the risk of cardiovascular disease. Wang et al **(Am J Pathol 2009, 174: 771–781)** hypothesized that HAART drugs mediate this effect by impairing endothelial function. Studies demonstrated that treatment of porcine pulmonary arteries with HAART drugs individually and in combination resulted in a lower vasorelaxation response, lower endothelial nitric oxide synthase levels, and higher levels of oxidative stress. Therefore, HAART drugs may play a role in the high incidence of pulmonary artery hypertension in HIV-infected patients.

Neprilysin Protects against Hypoxic Pulmonary Hypertension

Neprilysin, a protein expressed within the lung vasculature, breaks down neuropeptides that regulate both growth and contraction of smooth muscle cells. Vascular remodeling through smooth muscle cell growth and proliferation contributes to the severity of chronic hypoxic pulmonary hypertension (PHTN). To determine whether depletion of neprilysin increased susceptibility to PHTN in response to chronic hypoxia, Dempsey et al **(Am J Pathol 2009, 174: 782–796)** generated a mouse model deficient in neprilysin. Although neprilysin deficiency had minimal effects on baseline cardiac and pulmonary function, on hypoxic exposure, neprilysin-deficient mice had an augmented pulmonary hypertensive response. In addition, Dempsey and colleagues observed increased proliferation of pulmonary smooth muscle cells in these mice, which was reduced on reintroduction of neprilysin. Thus, introduction of neprilysin into the lungs of PHTN patients may provide a novel treatment for PHTN.

Neurodegeneration Can Be Caused by Cell Proliferation

The causes of cell death in neurodegenerative pathologies such as Alzheimer's and Parkinson's diseases are incompletely understood. Mature neurons in healthy individuals are postmitotic and quiescent; however, degenerating neurons up-regulate c-Myc (Myc), a cell-cycle regulatory protein and oncogene. This led Lee et al **(Am J Pathol 2009, 174: 891–897)** to hypothesize that cell cycle re-entry contributes to neurodegenerative pathogenesis. They found that expression of Myc in forebrain neurons resulted in re-entry of the cell cycle, as determined by expression of cell-cycle markers and DNA replication. Furthermore, Myc expression resulted in neural cell death, gliosis, and cognitive defects. Neurodegeneration, therefore, may be a disease of dysregulated cell-cycle control, and cell-cycle regulators should be explored as future treatment targets.

A New Model for Plague Vaccine Studies

Pneumonic plague is the most virulent form of infection caused by *Yersinia pestis*. Multiple animal models must be used to evaluate the efficacy of plague vaccines because human clinical trials that test new vaccines are not feasible. Anderson et al **(Am J Pathol 2009, 174: 910–921)** propose using Brown Norway rats as an alternate model to mice for studying plague vaccine performance because of their larger size and epidemiological association with *Y. pestis* infection. These rats succumb to pneumonic plague rapidly, within 2 to 4 days, with similar disease progression as in humans. Brown Norway rats could be protected from disease by vaccination with either the protective antigen LcrV or its mutant derivative V10. These rats also produced neutralizing antibodies specific to multiple epitopes on LcrV. These results validate the use of Brown Norway rats to study plague pathogenesis and immunity.

High Cholesterol Increases Tumor Angiogenesis and Promotes Progression in Prostate Cancer

Dietary cholesterol has been linked to the progression of prostate cancer. To determine whether high circulating cholesterol levels promote the growth of prostate tumors, Solomon et al **(Am J Pathol 2009, 174: 1017–1026)** examined the effects of hypercholesterolemia on tumor progression in a human prostate cancer xenotransplantation model in the presence and absence of Ezetimibe, a cholesterol uptake-blocking drug. They found that high serum cholesterol levels induced by a high-fat/high-cholesterol Western diet promoted tumor growth and that Ezetimibe could inhibit this increased tumor growth. High circulating cholesterol levels also affected angiogenesis, resulting in increased microvessel density and other in-

dicators of vascularity. This increase in angiogenesis was blocked by Ezetimibe treatment, possibly through up-regulation of the angiogenesis-inhibiting molecule thrombospondin-1. These data suggest that reducing serum cholesterol levels may inhibit prostate cancer growth specifically by inhibiting tumor angiogenesis.

Hemorrhage-Associated Macrophages (HA-mac) Are Atheroprotective

Conventional lipid-scavenging macrophages in atherosclerotic lesions exacerbate disease through the secretion of pro-inflammatory cytokines; however, macrophages found in hemorrhaged atherosclerotic plaques secrete the atheroprotective cytokine IL-10. Boyle et al (Am J Pathol 2009, 174: 1097–1108) examined the macrophage phenotype in hemorrhaged atherosclerotic plaques and found a novel population of macrophages, HA-macs, that expressed high levels of CD163, the macrophage scavenger receptor that binds hemoglobin-haptoglobin (HbHp), and low levels of HLA-DR. These HA-macs caused less oxidative damage and produced lower levels of hydrogen peroxide and superreactive oxygen species than conventional pro-atherogenic macrophages. HA-mac differentiation was driven by both HbHp and IL-10 expression and could be reproduced *in vitro*. Skewing macrophage differentiation to atheroprotective HA-mac may comprise a new cardioprotective therapeutic strategy.