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This Month in *AJP*

Hyperploidy Contributes to Cell Death in Alzheimer's Disease

Although a low-level of aneuploidy, an abnormal number of chromosomes, may contribute to neuronal diversity, high levels of aneuploidy may result in developmental abnormalities and disease. Ardendt et al (Am J Pathol 2010, 177:15–20) explored the effects of hyperploidy, having greater than the normal number of chromosomes, in Alzheimer's disease pathogenesis. They identified increased numbers of hyperploid cells in preclinical stages of Alzheimer's disease and showed that hyperploid neuronal cells in Alzheimer's disease have decreased viability and selectively higher levels of cell death than normal neuronal cells. These results highlight hyperploidy, perhaps as a result of a failure of neuronal differentiation, as a critical pathogenic event in neurodegeneration.

Noninvasive Detection of Injury in the Iris Vasculature

Early detection of uveitis could promote timely treatment and prevent irreversible tissue damage in the eye. To detect acute anterior chamber inflammation, a major cause of vision loss, Xie et al (Am J Pathol 2010, 177: 39–48) injected carboxylated fluorescent microspheres conjugated with recombinant P-selectin glycoprotein ligand-1 (rPSGL-1), which binds the leukocyte-adhesion molecule P-selectin, into endotoxin-induced uveitic animals. These microspheres adhered at similar levels as leukocytes, with increased adhesion in iritic animals and decreased adhesion in animals treated with topical anti-inflammatory drugs, allowing for quantification of the endogenous immune response. As microvessel accumulation preceded clinical signs of disease, this noninvasive imaging technique may provide a model system for studying the early stages of anterior uveitis.

Novel Mechanism of Neutrophil Adhesion

Leukocytes are targeted to sites of inflammation and infection via adhesive molecules, such as integrins, that are up-regulated on the surface of blood vessels. To determine whether sphingosine kinase-1 contributes to integrin-mediated neutrophil recruitment, Sun et al (Am J Pathol 2010, 177:436–446) examined tumor necrosis factor-α–mediated inflammatory responses on human umbilical vein endothelial cells under shear stress. Tumor necrosis factor-α activated $\alpha_5\beta_1$ integrin without altering β_1 integrin protein levels in a sphingosine kinase-1-dependent manner, although this effect was independent of the downstream sphingosine-1-phosphate family of G protein-coupled receptors. In addition, neutrophil adhesion in this system could be blocked by inhibiting either $\alpha_5\beta_1$ integrin or its ligand angiopoietin-2. Taken together, these data support sphingosine kinase-1 as a broad-spectrum target for inhibiting neutrophil recruitment and subsequent inflammatory and immune disorders.

Resveratrol Inhibits Angiogeneis

The phytoalexin resveratrol, a natural plant antimicrobial found in grapes, has been shown to decrease the signs of aging and act as an anticancer agent in model systems through the actions of sirtuin family proteins. To investigate the effects of resveratrol on angiogenesis, a key process in cancer progression, Khan et al (Am J Pathol 2010, 177:481–492) assessed the role of resveratrol on aberrant vascular proliferation *in vitro* and *in vivo*. Interestingly, resveratrol inhibited angiogenesis via a sirtuin-independent pathway. Furthermore, resveratrol treatment affected protein translation components by activating eukaryotic elongation factor-2 kinase and inhibiting elongation factor-2; inhibiting kinase activity reversed the angiogenesis-inhibiting function of resveratrol. These data suggest a novel pathway involved in angioproliferative diseases as well as a putative therapeutic strategy to treat these diseases.

Neutrophils Are Present in Atherosclerotic Plaques

Although monocytes and T lymphocytes have been shown to play important roles in atherogenesis, the contribution of neutrophils, the most abundant white blood cell in circulation, remains unclear. Therefore, Rotzius et al (Am J Pathol 2010, 177:493–500) examined a mouse model of atherosclerosis with fluorescent neutrophils and monocytes. They found that neutrophils accumulate in atherosclerotic lesions, although at lower levels than monocytes, and that neutrophilic accumulation occurs primarily in the high inflammatory shoulder regions of plaques. Moreover, neutrophils are the predominant immune cells that interact with endothelial cells in the shoulder regions of atherosclerotic plaques, suggesting that these cells may play a hitherto unappreciated role in the immunological processes of atherogenesis.