The American Journal of Pathology, Vol. 177, No. 5, November 2010

DOI: 10.2353/ajpath.2010.100904

This Month in *AJP*

Omega-3 Fatty Acids Prevent Muscle Degeneration in Muscular Dystrophy

Muscular dystrophies are degenerative neuromuscular disorders with limited treatment options. To determine whether a diet rich in ω-3 fatty acids could affect muscular degeneration, Fiaccavento et al (Am J Pathol 2010, 177:2176–2184) examined a hamster model of neurodegeneration. A diet enriched in flaxseed-derived ω-3 α-linolenic fatty acid prevented muscle degeneration in this model. Furthermore, the ω-3-enriched diet led to both morphological and function improvement of myocytes as well as myocyte proliferation to repair damaged muscle. These findings suggest that diet may be a viable treatment strategy to ameliorate muscular dystrophy.

Toll-Like Receptors (TLRs) Limit Herpes Simplex Virus 1 (HSV-1) Infection

HSV-1 infection is widespread and often asymptomatic; however, infection may result in fatal encephalitis. Although innate immunity plays a key role in controlling HSV-1 infection, the specific role of individual TLRs remains unknown. Using a murine model of intranasal HSV-1 infection, Lima et al (Am J Pathol 2010, 177:2433–2445) found that mice deficient in either TLR 9 or double deficient in TLR 2 and TLR 9 were more susceptible to infection than control animals. Cytokine and chemokine expression levels were altered in both the trigeminal ganglia and brains of these animals compared with control animals. Thus, HSV-1 infection is likely controlled in a TLR-dependent mechanism in the trigeminal ganglia of infected individuals.

Insulin-Like Growth Factor 2 Receptor (IGF2R) in HIV Encephalitis (HIVE)

IGF2R, which functions by removing growth factors from both tissues and blood via direct lysosomal targeting, is highly expressed in microglial nodules of individuals affected by HIVE. However, due to perinatal lethality of models deficient in IGF2R, the function of IGF2R in the CNS remains unknown. Suh et al (Am J Pathol 2010, 177:2446–2458) hypothesized that IGF2R positively regulated HIV infection in the CNS. *In vitro*, IGF2R expression was up-regulated as a result of interferon-γ signaling, and IGF2R was shown to increase levels of HIV infection in brain-derived cells, including microglia. Moreover, RNAi-mediated depletion of IGF2R increased levels of the inflammatory chemokine IP-10 in infected cells. IGF2R may therefore provide a novel therapeutic target for HIV/AIDS.

Microglia in Alzheimer's Disease

Alzheimer's disease is a neurodegenerative disorder characterized by neuroinflammation and the deposition of β-amyloid (Aβ) plaques. Microglia, resident inflammatory cells in the brain, are activated in Alzheimer's disease patients; however, the role microglia play in Alzheimer's disease pathology may vary depending on local conditions. Lee et al (Am J Pathol 2010, 177:2549–2562) discovered that models of Alzheimer's disease that lacked CXC3R1, the receptor for the chemokine CXC3L1, had reduced levels of Aβ deposition and a decrease in the number of resident microglia. Microglia in these mice expressed altered levels of chemokines and cytokines, and CXC3L1-CXC3R1 signaling reduced microglial phagocytic capacity. Therefore, CXC3R1 deficiency leads to enhanced phagocytic clearance of Aβ by microglia.

Mutations in Mesenchymal Stem/Progenitor Cells May Lead to Soft Tissue Sarcomas

Soft tissue sarcomas affect nonepithelial and extraskeletal tissues such as muscles, blood vessels, and nerves; however, the pathogenesis of this disease remains poorly understood. To explore what role two tumor suppressor genes frequently mutated in human soft tissue sarcomas, *p53* and *Rb*, play in disease initiation, Choi et al (Am J Pathol 2010, 177:2645–2658) developed a model with inducible deficiency in these genes. Upon deletion, these mice developed soft tissue sarcomas, and disease development was dependent on local mesenchymal stem/progenitor cells and not bone marrow–derived cells. Therefore, dermal mesenchymal stem/progenitor cells may be the primary cell type affected by *p53* and *Rb* mutation, resulting in soft tissue sarcomas.