Tips from the American Journal of Pathology

EurekAlert

Inflammasome Increases Muscle Damage in Muscular Dystrophy

Dr. Kanneboyina Nagaraju and colleagues at the Children's National Medical Center, Washington, DC demonstrate that affected muscle may directly contribute to inflammation in muscular dystrophy. Their report can be found in the June 2010 issue of The *American Journal of Pathology*.

Muscular dystrophy is a group of genetic diseases that result in progressive weakening of the human body, leading to muscle wasting and even the inability to walk. Many patients with muscular dystrophy shown signs of inflammation; however, the mechanisms governing this inflammation in disease pathogenesis remain unexplored.

To investigate the role of the inflammasome, which is responsible for activation of inflammatory processes, in muscular dystrophy, Rawat et al examined the inflammasome platform in mouse and human tissues that develop limb girdle muscular dystrophy type 2B (LGMD2B). They found that components of the inflammasome pathway were upregulated and activated in diseased muscle as compared with control muscle and that primary skeletal muscle cells can secrete inflammatory mediators, directly participating in inflammasome formation. Moreover, diseased muscle cells expressed innate immune molecules, suggesting that affected muscle may directly contribute to inflammation in muscular dystrophy and providing a new therapeutic target for LGMD2B.

Dr. Nagarju's group concludes that "it is likely that age-related physiological changes in the skeletal muscle, together with environmental insults, can initiate the disease process in LGMD2B. ? [They] propose that the increase in vesicular trafficking and plasma membrane repair defects associated with LGMD2B results in the release of ATP and other endogenous danger/alarm signals (e.g, HMGB1, S100 proteins). These molecules, in turn, bind to their cellular receptors (toll-like receptors, P2X7 receptors) and activate the inflammasome pathway. ? Downstream processes [may then] activate not only inflammation and fibrosis but also lead to significant muscle fiber damage and dysfunction."

Rawat R, Cohen TV, Ampong B, Francia D, Pons A, Hoffman EP, Nagaraju K: Inflammasome up-regulation and activation in dysferlin-deficient skeletal muscle. *Am J Pathol* 2010, 176: 2891-2900

New Model for Chronic Wasting Disease

A group led by Dr. Edward Hoover at Colorado State University, Fort Collins, CO have generated a mouse model of cervid chronic wasting disease. They present

these findings in the June 2010 issue of The *American Journal of Pathology*.

Chronic wasting disease is a fatal prion-induced disease, similar to mad cow disease, that affects cervids such as deer, elk, and moose. It is a neurodegenerative disease typified by chronic weight-loss leading to death. Prions are infectious agents composed primarily of proteins that are thought to be propagated by transmitting a mis-folded protein state. Due to the lack of an appropriate small animal model, little is known about cervid chronic wasting disease.

Using a mouse model of chronic wasting disease that expresses cervid prion protein (PrP), Seelig et al examined the susceptibility, pathogenesis, and transmission of cervid chronic wasting disease. They found that cervid PrP^{C} (protease-sensitive PrP) was expressed in a number of different tissues, including lymphoid, nervous, hematopoietic, endocrine, and certain epithelial tissues, in this model. Additionally, disease could be transferred by various infectious methods, including injection into the brain, blood stream, and gut. It could also be transmitted orally, although the oral route required a larger infecting dose. Furthermore, this disease could be transferred between animals without experimental intervention to uninfected mice, highlighting the suitability of this system in studying cervid transmissible spongiform encephalopathy.

Dr. Hoover's group suggests that "cervidized transgenic mice substantially recapitulate the clinical, neuropathologic, and PrP^{RES} tropism and transmission patterns reported in the native cervid species and [that] studies in Tg[CerPrP] mice can provide additional insights into the trafficking, shedding, and lateral transmission of [chronic wasting disease] prions."

Seelig DM, Mason GL, Telling GC, Hoover EA: Pathogenesis of Chronic Wasting Disease in Cervidized Transgenic Mice. *Am J Pathol* 2010 176: 1785-2797

New Target May Inhibit Metastatic Breast Cancer

Researchers led by Dr. Yves St-Pierre at INRS-Institut Armand-Frappier, Québec, Canada implicate galectin-7 as a breast cancer differentiation marker. They report their data in the May 2010 issue of The *American Journal of Pathology*.

Breast cancer is the second-most common type of non-skin cancer and the fifth-most common cause of cancer death world-wide. Breast cancer is 100-times more common in women than in men.

The protein galectin-7, which leads to cell death, is expressed in and plays a metastatic role in various types of cancer. To determine the role of galectin-7 in breast cancer, Demers et al investigated galectin-7 expression and function in breast cancer cells. Galectin-7 was highly expressed in two pre-clinical models of breast cancer, and high galectin-7 expression levels increased the metastatic potential of these tumor cells. In humans, high expression levels of galectin-7 were restricted to high-grade tumors and were associated with metastasis. Taken together, these data implicate galectin-7 as both a breast cancer differentiation

marker and a potential therapeutic target for metastatic breast cancer.

Dr. St.-Pierre and colleagues "believe that lower survival rates and increased metastases in mice injected with breast cancer cells overexpressing galectin-7 are related to the ability of galectin-7 to protect from apoptosis, as previously shown in the case of galectin-3. ? Further studies regarding the role of galectin-7 in resistance to apoptosis are currently under investigation."

Demers M, Rose AAN, Grosset A-A, Biron-Pain K, Gaboury L, Siegel PM, St-Pierre Y: Overexpression of galectin-7, a myoepithelial cell marker, enhances spontaneous metastasis of breast cancer cells. *Am J Pathol* 2010, 3023-3031

Low Caveolin-1 Expression Contributes to Lung Disease

Dr. Craig Henke and colleagues at the University of Minnesota, Minneapolis, MN propose that low levels of caveolin-1 contribute to the over-proliferation of fibroblasts in lung disease. These results are presented in the June 2010 issue of The *American Journal of Pathology*.

Idiopathic pulmonary fibrosis (IPF) is a form of lung disease characterized by lung fibrosis, or development of excessive connective tissue resulting in lung damage, of unknown origin. Low levels of PTEN (phosphatase and tensin homolog), a molecule that prevents cells from growing and dividing too rapidly, have been implicated in the over-proliferation of fibroblasts following tissue injury. However, the molecular mechanisms underlying the low expression of PTEN in lung fibroblasts in IPF remain to be determined.

Xia et al hypothesized that caveolin-1, a molecule involved in cell signaling and intake of external molecules that is decreased in fibroblasts in IPF patients, may be responsible for the levels of PTEN expression in these cells. They correlated low levels of caveolin-1 and PTEN expression and demonstrated that overexpression of caveolin-1 restored PTEN expression in IPF fibroblasts. Indeed, PTEN interacted with caveolin-1 through its caveolin-1 binding sequence. Decreased caveolin-1 expression therefore facilitates the over-proliferation of fibroblasts in IPF.

Dr. Henke's group "demonstrate[s] that in IPF fibroblasts, a lack of caveolin-1 expression in the plasma membrane reduces membrane-associated PTEN levels and activity. ? This confers IPF fibroblasts with a phenotype characterized by the ability to circumvent the proliferation-suppressive properties of polymerized type I collagen."

Xia H, Khalil W, Kahm J, Jessurun J, Kleidon J, Henke CA: Pathologic Caveolin-1 Regulation of PTEN in Idiopathic Pulmonary Fibrosis. *Am J Pathol* 2010, 176: 2626-2637

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