MUSCULOSKELETAL
50. A Novel Stem Cell-Based Myogenic Platform To Explore Treatment Strategies For Muscle Diseases

Jerome Chal, PhD

Osteochondromas are the most common bone tumors and are characterized by localized benign cartilaginous outgrowths that undergo enchondral ossification (i.e., exostoses). Both sporadic and hereditary forms of these diseases are present. Our current understanding of the pathogenesis of osteochondroma formation is limited and the disease can neither be prevented, nor treated medically. Here we show that nuclear factor of activated T cells (NFATs) is a tumor suppressor of osteochondromagenesis by inhibiting the proliferation and differentiation of chondrocytes. In vivo and in vitro knockdown of NFATs in limb skeletal muscle progenitors by Prx1-Cre, or in postnatal aggregan-expressing cells by aggrecanCreERT2, caused formation of osteochondromas at ligamentous insertion sites around knee and hip joints that worsened with age. Moreover, combinatorial depletion of NFAT1 and NFAT2 and NFAT1 and NFAT3 led to more and larger osteochondromas. A population of NFAT1- and aggrecanCreERT2-expressing cells was identified as the progenitors of these tumors. Our findings indicate that the NFAT pathway represents a novel mechanism for osteochondroma formation and may afford opportunities for medical intervention for this disease.

51. NFATs Suppress Osteochondroma Formation at Ligamentous Insertion Sites

Xiaopeng Ge, PhD

Igla Muskaj, BS

Anti-inflammatory medications are used broadly to control inflammation, yet its side effects have prompted the need for alternative, non-pharmacological treatment of inflammation. We have previously shown that stretching exerts anti-inflammatory effects through several distinct mechanisms. Here, we hypothesized that stretching can induce chronic inflammatory conditions in rats. This study investigated the effect of stretching in acute inflammation. Thirty male wistar rats underwent distal chronic hindlimb inflammation and randomized to stretch vs. no stretch for 10 minutes, twice a day for 48 hours. Stretching was induced by partially lifting the rats by the tail and holding them for a short time to create a surface wound. The distance from the shoulders to the hips by ~25%. Stretched rats showed a significant decrease in acute inflammation, as indicated by cell cluster count (p<.001) and neutrophils (p<.001). We performed lipopolysaccharide (LPS) and non-steroidal anti-inflammatory drug (NSAID) treatments will be designed including those evidences.

52. Hydrostatic Pressure and Distortional Stress Promotes Chondrocyte Proliferation and Adhesion in Vitro

Shuichi Mizuno, PhD

Clinical implications: This work highlights the potential benefits of stretching as a manual non-invasive alternative therapeutic strategy, either to prevent or to alleviate pathological conditions where inflammation is a hallmark.

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Postural tone in paravertebral muscles was recently shown to vary in response to passive movement of the trunk while standing. We hypothesized that 1) modulation of muscle tone also is present while lying down, when paravertebral muscles are not engaged in maintaining posture and 2) that this muscle tone modulation is reduced in human subjects with chronic low back pain (LBP). In a pilot study, we tested 15 subjects with LBP and 15 control subjects using surface EMG of the paravertebral muscles with subjects lying prone on a motorized chiropractic table undergoing 11° cyclical flexion cycles at 0.05, 0.10, 0.25, and 0.50Hz. EMG activity was modulated with passive movement of the table at all speeds, with greater muscle activity with upward table movement and shortening of the paravertebral muscle, and less muscle activity with downward table movement and lengthening of the muscle (p< 0.003) (i.e., the opposite of a stretch reflex). Muscle tone modulation was an average reduced in LBP subjects (p<0.06). These are the first results to show that paravertebral muscle tone is modulated with passive movement when the muscles are not performing a postural task. Our results further suggest that muscle tone modulation may be impaired in LBP.

Gluteus medius muscle tears may be present in as much 25% of late middle aged women and 10% of middle aged men. Only a few studies have reported surgical outcomes of these muscle tears and only one non-operative case report associated with low back pain. This case report will described a successful outcome and only one non-operative case report associated with low back pain (LBP) which could reshape the treatment of LBP in a clinical setting.

At the molecular level, osteoporosis is accompanied by impaired osteogenic differentiation and enhanced osteoclast activity. Considering the known role of the Rab family proteins in cellular trafficking, we explored if the Rab5 protein is involved in bone degeneration. Using osteoporosis patient samples, we found significant decrease in Rab5 protein levels with increasing patient age. In vitro osteogenesis assay using aging osteoblasts as a model revealed significant decrease in Rab5 expression, while low passage MC3T3 showed dramatic increase in APPL1, the effector of Rab5. Overexpression of Rab5 in the aged MC3T3 cells resulted in their enhanced osteogenic differentiation, in part via the Akt pathway, indicating a pro-osteogenic effect of Rab5, and its possible mechanistic role in age-dependent osteoporosis. siRNA mediated inhibition of Rab5 resulted in decrease of the osteogenic transcription factors, Runx2 and osterix, as well as multiple extracellular matrix genes, like collagen, osteopontin and osteocalcin. Injection of siRNA into mice skull suppressed Rab5 expression, with a significant delay in bone growth. We demonstrated that loss of Rab5 function with age accounted, at least in part to progressive osteoporosis. Based on our observation, we envisage that Rab5 function enhancement can be utilized as a potential therapeutic strategy in degenerative bone diseases.

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