RHEUMATOLOGY RESEARCH FOUNDATION

SUMMER RESEARCH SERIES

ADVANCES IN OSTEOARTHRITIS

FRIDAY, AUGUST 20TH
2:00 - 3:45 PM EDT

Bin Wang, PhD
Thomas Jefferson University

MAGI-3 as a New Target for Therapy of Osteoarthritis

Innovative Research Award

Osteoarthritis (OA) is a degenerative joint disease characterized by loss of articular cartilage and alterations in subchondral bone architecture. Parathyroid hormone-related protein (PTHrP) is a heterogeneous polypeptide with sequence homology to PTH. Both PTH and PTHrP bind to the type 1 PTH receptor (PTH1R). Signaling through the PTH1R maintains bone remodeling and regulates the articular chondrocyte phenotype under healthy conditions. PTH or PTHrP activates multiple signaling pathways but not all of them are anabolic. Both published as well as our preliminary data demonstrate a Gs/cAMP signaling arm that is therapeutic and a Gq/phospholipase C (PLC) signaling arm that is pathogenic. Systemic or intra-articular daily injection of PTH or PTHrP is able to prevent and treat OA. PTHrP is normally secreted by articular chondrocytes in low levels and is increased in OA. An alternative and superior strategy is to “tune” PTH1R signaling to preferentially activate the PTH1R therapeutic signaling arm, while avoiding its pathogenic signaling arm. Our preliminary data show that MAGI-3 (membrane-associated guanylate kinase with inverted orientation 3) is a novel PTH1R-interacting PDZ protein, and MAGI-3 expression in articular cartilage is reduced in human OA and in a mouse OA model. Beta-catenin mediates canonical Wnt signaling pathway and promotes chondrocyte hypertrophy. Recent data from our group and others have demonstrated that beta-catenin interacts with the PTH1R and switches PTH1R signaling from Gs/cAMP to Gq/PLC activation. Importantly, our preliminary data indicate that MAGI-3 exhibits higher binding affinity with PTH1R than that of beta-catenin with PTH1R, and exogenous MAGI-3 enhances PTHrP stimulation of cAMP formation and reduces PLC activity in chondrocytes. Based on these findings, the central hypothesis of this proposal is that MAGI-3 competes beta-catenin binding to the PTH1R to reverse the beta-catenin-mediated PTH1R signaling switch, and exogenous MAGI-3 can prevent/treat OA progression. Two specific aims will test this hypothesis. Aim 1 will characterize how MAGI-3 counteracts the beta-catenin-mediated PTH1R signaling switch and inhibits chondrocyte differentiation and apoptosis in vitro. Aim 2 will establish whether exogenous MAGI-3 protects against cartilage

damage in an in vivo OA model. The predictive results are that external control of MAGI-3 expression will prevent cartilage lesions and increase cartilage repair via shifting the PTH1R signaling toward its therapeutic pathway. Successful completion of these studies therefore constitutes important preclinical findings that would facilitate advancement of this work toward clinical trials of OA, and ultimate application in humans. The long-term goal of this project is to design cost-effective anabolic agents with less toxicity, and convenient use for the treatment of OA.

Ru L Bryan, PhD
University of California, San Diego

Inhibition of CD38 and Supplementation with Nicotinamide Riboside as Novel Approaches for Osteoarthritis

Innovative Research Award

Joint injury and aging are the major risk factors for development of osteoarthritis (OA), the most common form of arthritis and a leading cause of physical disability. There are not yet effective medical therapies to prevent or slow the disease process. Our long-term goal is to develop new rationally designed OA therapies that effectively target pathogenesis and suppress disease development and progression.

As OA progresses, failure of the synovial joint organ frequently develops, with degeneration of articular cartilage as a core disease feature. Chondrocytes, the sole cells in articular hyaline cartilage, are responsible for maintaining the homeostatic balance between extracellular matrix anabolism and catabolism. Dysfunction of chondrocytes in OA, amplified by local inflammatory processes, leads to cartilage degradation as a result of excessive chondrocyte catabolic activity. Mounting evidence indicates that maintenance of proper intracellular levels of nicotinamide adenine dinucleotide (NAD+), a key intermediate metabolite, is critical for maintaining tissue homeostasis. This is because NAD+ is a cofactor for numerous enzymes involved in cellular energy metabolism and adaptive responses of cells to bioenergetics and oxidative stress. NAD+ levels steadily decline with age, associated with increased expression of CD38, the main NADase in mammalian tissues. The changes in NAD content are reflected in altered activities NAD-dependent enzymes such as sirtuins, thereby leading to changes in cellular metabolism, gene expression and protein function. Our preliminary studies reveal that NAD+ decline was associated with increased CD38 expression and activity in human knee chondrocyte and cartilage of OA and aged donors and in chondrocytes stimulated with IL-1Î². Inhibition of CD38 by its inhibitor apigenin in human OA chondrocytes diminished NADase activity, raised NAD+ levels, improved mitochondrial function, prevented excessive oxidative stress, and attenuated chondrocyte and cartilage catabolic responses to IL-1Î², likely via SIRT1 and SIRT3 signaling. Treatment of human OA chondrocytes with NAD+ precursor nicotinamide riboside (NR) also led to increase in NAD+ levels and attenuation of chondrocyte and cartilage catabolic responses to IL-1Î². These data suggest that maintaining a proper chondrocyte NAD+ content is critical for cartilage homeostasis.

Based on these findings, in this translational project, we propose to conduct preclinical studies testing our central hypothesis that NAD+ decline contributes to cartilage degradation after joint injury and spontaneously during aging, and restoration of NAD+ levels limits OA development and progression in mice in vivo. Using mouse experimental OA model of both injury-induced OA through destabilization of medial meniscus (DMM) and age-related spontaneous OA, we will test the hypothesis that CD38 deficiency or repletion of NAD+ protect mice from OA development and progression. We will test if CD38 knockout mice and mice received treatment with pharmacological NAD+ boosters (CD38 inhibitor apigenin and NAD+ precursor NR) display little or reduced OA phenotype. We will further test for association of sustained joint tissue NAD+ levels and cartilage expression of SIRT1, SIRT3 and their downstream targets that are important for maintaining mitochondrial function, limiting oxidative stress, and preventing excessive matrix catabolism.
Completion of these studies will provide new insights into how critical NAD+ metabolism influences cartilage tissue integrity in aging and after joint injury. In this regard, our proof-of-concept study that restoration of NAD+ levels suppresses OA development and progression provides a translational approach to help develop and test novel medical treatment for OA.

Elizabeth Wellsandt, PhD, DPT
University of Nebraska Medical Center

Role of Biomarkers in the Osteoarthritis Pathway After Joint Injury

Investigator Award

Posttraumatic osteoarthritis (PTOA) is rapidly becoming a major rheumatology concern in younger adults. Within ten years, 50% of individuals with an anterior cruciate ligament (ACL) injury develop PTOA, which is directly contributing to a 76% increase in recent total knee replacement surgeries among Americans aged 20-49 years. Younger adults with PTOA will live with this chronic disease for much longer than previous generations, resulting in substantial societal and personal burden. However, evidence-based interventions to prevent PTOA do not exist, and no prognostic clinical markers are available to identify patients most at risk for PTOA development. Our long-term goal is to prevent PTOA after knee injury before irreversible degenerative processes occur. We know that within months of ACL injury, a cascade of changes in biochemical markers and articular cartilage microstructure (such as T2 relaxation) indicate negative joint alterations. Therefore, the purpose of this study is to determine associations between knee joint loading after ACL injury with biochemical and structural signs of joint degeneration. Our central hypothesis is that lower levels of joint loading after ACL injury are associated with markers of joint breakdown. Our first aim will determine the range of healthy knee joint loading after ACL injury by correlating physical activity levels and gait biomechanics with serum and synovial fluid biomarkers of cartilage degeneration, bone resorption, and joint inflammation. Our second aim will develop a prognostic model of PTOA for future clinical application by correlating demographic, biochemical, physical activity,

biomechanical, and clinical measures with increased T2 relaxation time (as a marker of future PTOA). The prognostic factors that emerge from this study will inform the development of a future clinical tool to identify patients at high risk for PTOA who may benefit from novel rehabilitation approaches that optimize total daily joint loading to prevent or delay PTOA after knee injury.

Chenchen Wang, MD MSc
Tufts Medical Center

Neurobiological Mechanisms of Mind-body Therapy for Knee Osteoarthritis

Innovative Research Award

This proposal aims to provide crucial knowledge of the neurobiological mechanisms underlying Tai Chi mind-body therapy for knee osteoarthritis (OA). Knee OA is a leading cause of long-term pain and disability for which no effective medical treatments currently exist. Our recent trials showed that Tai Chi for knee OA produced clinical improvements in pain and function after 12 weeks of intervention, with benefits maintained up to 12 months. However, limited knowledge of the underlying mechanisms has restricted the understanding and further development of this promising therapy.

Accumulating evidence suggests that the central nervous system is involved in the pathophysiology of OA pain. Neuroimaging studies found patients reporting higher levels of chronic OA pain have greater opioid receptor availability in the striatum and regions of the descending opioidergic pathway, indicating functional alteration in the descending pain modulation system. The long-term objective of our research is to provide theoretical and empirical evidence to optimize the effects of Tai Chi for patients with knee OA. The aim of this study is to investigate the central mechanism of knee OA pain using brain imaging technology to evaluate how brain function and structure change in response to mind-body exercise over time. We hypothesize Tai Chi may work by modulating the interaction among cognitive control network, default mode network, descending pain modulation system, limbic system, salient network, and sensory motor system through complex mind-body interactions.

By combining multiple brain imaging modalities measurements, we will examine the neural substrates of Tai Chi compared with wellness education in adults with knee OA. We will randomize 60 eligible individuals who meet the American College of Rheumatology criteria for knee OA into Tai Chi or wellness education interventions for 12 weeks. We will compare changes in resting state functional connectivity of the cognitive control network, and functional magnetic resonance imaging responses to pressure pain, brain morphometry, as well as their association with clinical outcomes.

Results of this innovative mechanistic study will have important therapeutic implications and provide critical insight into the clinical, behavioral, and neurobiological mechanisms of the potential disease-modifying role of mind-body therapies for knee OA. The findings will lead to the establishment of a new treatment paradigm in OA and have broad application to the management of chronic musculoskeletal pain.

We hope you will join us. Registration is required.

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