INDIGO (EU-India multilateral research calls), Authors acknowledge EC of INNO-INDIGO for the funds.

Disclosure of Interests: None declared


FR00512

RETRO-INVERSO TAT-BECLIN-1 INDUCES SYNOVIAL FIBROSIS AND DOES NOT PROTECT CARTILAGE FROM DEGENERATION IN A MOUSE MODEL OF OA

Jason Rockel, Brian Wu, Sayaka Nakamura, Evgeny Rossmann, Mohit Kapoor. University Health Network, Toronto, Canada

Background: Beclin-1 is a component of the autophagy pathway necessary for formation of autophagosomes, contributing to autophagy-mediated cellular homeostasis. Enhancing autophagy through inhibition of mTOR activity, either via genetic deletion in chondrocytes or intra-articular injection of rapamycin, attenuates progression of surgically-induced models of osteoarthritis (OA). Retro-inverso TAT-Beclin-1 is a cell-permeable peptide which competes for binding to the endogenous Beclin-1 inhibitor GAPP-R1, thus promoting autophagy. It is unknown whether activation of Beclin-1 is sufficient to protect joints from osteoarthritis progression.

Objectives: For this study, we sought to determine if retro-inverso TAT-Beclin-1 could attenuate OA progression in a surgically-induced mouse model.

Methods: Eight-week old C57BL/6 mice underwent destabilization of the medial meniscus (DMM) surgery to induce OA, or sham surgery as a control. Mice were injected intra-articularly with retro-inverso TAT-Beclin-1 (2 mg/kg in 5 µl) twice weekly for 2 or 9 weeks. Mice were sacrificed at 10-weeks post-surgery. Knee joints were stained with Safranin-O/Fast green to evaluate cartilage degeneration and Masson’s trichrome to determine degree of synovitis using OARSI scoring for mice. Sections were stained for α-SMA (myofibroblast) and CD45 (hematopoietic-origin cell) to evaluate changes in markers of fibrosis and inflammation, respectively.

Results: As opposed to the effects of mTOR deletion in cartilage or rapamycin treatment in joints, injection of retro-inverso TAT-Beclin-1 for 2 into knee joints of mice with DMM-induced OA had no effect on the degree of articular cartilage degeneration in the tibia or femur as compared to PBS-injected controls. However, in both sham and DMM mice, retro-inverso TAT-Beclin-1 for 2 or 9 weeks of treatment induced a pronounced thickening of the synovium with increased cell numbers and collagen deposition compared to PBS-treated mice. The increased number of synovial cells in 2-week treated mice did not show substantial expression of α-SMA or CD45+ cells, suggesting the increased number of cells and matrix in the synovium was independent of myofibroblast differentiation or inflammatory influx.

Conclusion: Contrary to our expected results, retro-inverso TAT-Beclin-1 did not attenuate cartilage degeneration. Rather, it promoted substantial synovial thickening that likely involved cell proliferation and collagen deposition. This severe fibrotic phenotype appears independent of myofibroblast differentiation or inflammation, normally associated with typical fibrotic responses. To evaluate the potential for dose responses with retro-inverso TAT-Beclin-1 in synovial joints, we are currently modifying our dosing strategy in an effort to determine possible disease modifying effects of this novel Beclin-1 activator.

Disclosure of Interests: None declared


FR00513

HISTONE-ACYTYLTRANSFERASES CBP AND P300 REGULATE AUTO PHAGY AND PROTEASOMAL DEGRADATION IN SYNOVIAL FIBROBLASTS

Monika Krozel1,2, Marcel Gabathuler1, Christoph Kolling1, Kerstin Klein1,2, Robert Menar1,2, Alexander Woisetschlaeger1,2, Jure Khazan1,2, Martin Zavodovsky1,2, Eugene Papichev1,2, Kerstin Klein1,2, Monika Krosel1,2, Marcel Gabathuler1, Christoph Kolling3, Matija Tomsic2, Monika Krosel1,2

Background: Beclin-1 is a component of the autophagy pathway necessary for formation of autophagosomes, contributing to autophagy-mediated cellular homeostasis. Enhancing autophagy through inhibition of mTOR activity, either via genetic deletion in chondrocytes or intra-articular injection of rapamycin, attenuates progression of surgically-induced models of osteoarthritis (OA). Retro-inverso TAT-Beclin-1 is a cell-permeable peptide which competes for binding to the endogenous Beclin-1 inhibitor GAPP-R1, thus promoting autophagy. It is unknown whether activation of Beclin-1 is sufficient to protect joints from osteoarthritis progression.

Objectives: For this study, we sought to determine if retro-inverso TAT-Beclin-1 could attenuate OA progression in a surgically-induced mouse model.

Methods: Eight-week old C57BL/6 mice underwent destabilization of the medial meniscus (DMM) surgery to induce OA, or sham surgery as a control. Mice were injected intra-articularly with retro-inverso TAT-Beclin-1 (2 mg/kg in 5 µl) twice weekly for 2 or 9 weeks. Mice were sacrificed at 10-weeks post-surgery. Knee joints were stained with Safranin-O/Fast green to evaluate cartilage degeneration and Masson’s trichrome to determine degree of synovitis using OARSI scoring for mice. Sections were stained for α-SMA (myofibroblast) and CD45 (hematopoietic-origin cell) to evaluate changes in markers of fibrosis and inflammation, respectively.

Results: As opposed to the effects of mTOR deletion in cartilage or rapamycin treatment in joints, injection of retro-inverso TAT-Beclin-1 for 2 into knee joints of mice with DMM-induced OA had no effect on the degree of articular cartilage degeneration in the tibia or femur as compared to PBS-injected controls. However, in both sham and DMM mice, retro-inverso TAT-Beclin-1 for 2 or 9 weeks of treatment induced a pronounced thickening of the synovium with increased cell numbers and collagen deposition compared to PBS-treated mice. The increased number of synovial cells in 2-week treated mice did not show substantial expression of α-SMA or CD45+ cells, suggesting the increased number of cells and matrix in the synovium was independent of myofibroblast differentiation or inflammatory influx.

Conclusion: Contrary to our expected results, retro-inverso TAT-Beclin-1 did not attenuate cartilage degeneration. Rather, it promoted substantial synovial thickening that likely involved cell proliferation and collagen deposition. This severe fibrotic phenotype appears independent of myofibroblast differentiation or inflammation, normally associated with typical fibrotic responses. To evaluate the potential for dose responses with retro-inverso TAT-Beclin-1 in synovial joints, we are currently modifying our dosing strategy in an effort to determine possible disease modifying effects of this novel Beclin-1 activator.

Disclosure of Interests: None declared


FR00514

NEW DIAGNOSTIC BIOMARKER OF BONE TISSUE METABOLISM DISORDERS IN RHEUMATOID ARTHRITIS

I. Sperwonska1, J. Polakowka, B. Zawadowsky1,2, Eugene Papichev1,2, Akhverdyan Yury1

Background: Bone mineral density and proteins/peptides determination in blood and urine as markers of bone resorption and formation are currently used to diagnose osteoporosis (OP) and metabolic bone diseases. However, these methods have some disadvantages for bone turnover evaluation. Recent evidence suggests that in RA changes in the secretion of hormones of white adipose tissue can be revealed [1,2,3,4]. One of them is Adiponectin possessing anti-inflammatory, anti-diabetic and anti-atherogenic properties. Changes in Adiponectin levels may reflect influence of immune inflammation on bone turnover.

Objectives: To study the clinical and diagnostic value of serum Adiponectin determination in RA patients complicated by OP.

Methods: We examined 88 women with documented diagnosis of RA and mean disease duration of 6.56±0.88 years. We used EULAR/ARA 2010 criteria to diagnose the patients. Female patients with II degree of disease activity (DAS28), Steinbrocker stage II (erosive), rheumatoid factor- and anti-cyclic-citrullinated peptide antibody-positive were prevalent. We excluded patients who had surgery or developed an infection within the last 8 weeks, pregnant and breast-feeding women, those with severe heart, liver or kidney disease, immune deficiency, leukopenia or chronic infection. A control group of 45 healthy females aged of 25 and 55 years were included in the study. There were no reported findings of

Disclosure of Interests: None declared
