Background: Cystatins are cysteine proteases-inhibitors secreted by Fasciola hepatica in order to modulate the host immune response to promote survival of the parasite. These molecules are able to inhibit different mammal cathepsins, to regulate the immune balance via Th2 and T regulatory responses, to downregulate antigen presentation and the release of pro-inflammatory cytokines (1,2). - mechanisms that are important in the development and maintenance of several immunopathology, as rheumatoid arthritis (RA) (3).

Objectives: To evaluate the therapeutic effect of recombinants cystatin 1 and cystatin 3 from Fasciola hepatica in a mice model of collagen-induced arthritis (CIA). Methods: Twenty-seven DBA/1J mice were induced with CIA by an injection of collagen type-II and Freund’s adjuvant at days 0 and 18. Animals were randomely divided into three groups: vehicle (n=9, treated with 100 μg/dose of recombinant cystatin 1) and cystatin 1 (n=9, treated with 100 μg/dose of recombinant cystatin 3). Treatment started after day 18 by intraperitoneal injection once a day until the end of the experiment, at day 45 after CIA induction. Clinical arthritis score, nociception, paw edema, body and spleen weight were evaluated. Lymphocytes were isolated from lymph nodes and CD4+CD25+Foxp3+ T regulatory subset was assessed by flow cytometry. Data are expressed as mean ± SEM and were evaluated by one-way or two-way ANOVA followed by Bonferroni post-test.

Results: Treatment with cystatin 1 did not alter any of the analyzed parameters. On the other hand, cystatin 3 was able to reduce clinical arthritis score from day 38 with 32% of reduction at day 45 (9.2±2.12 vs 2.7±0.32, p<0.05). In addition, treatment with cystatin 3 diminished nociception (cystatin 3: 4.0±0.36g, vehicle: 2.7±0.32g) (p<0.05) and paw edema (cystatin 3: 63.38±3.66%; vehicle: 58.31±6.77%)

Conclusion: Treatment with cystatin 3 improved collagen-induced arthritis by attenuating the disease score, nociception and paw edema. Moreover, the treatment did not induce body weight loss or spleen weight alteration. These results suggest that recombinant cystatin 3 from Fasciola hepatica has the potential as a treatment for inflammatory and autoimmune diseases such as RA.

References:

Disclosure of Interests: Miran Farinon: None declared, Renata Ternus Pedo: None declared, Thaís Heim da Rosa: None declared, Barbara Jonson Bartikoski: None declared, M. Farinon1,2, R. T. Pedo1,2, T. Hein Da Rosa1,2, B. Jonson Bartikoski1,2, M. Canelca1, H. Bunselmyer Ferreira1, R. Xavier1,4, M. Doenças Autoimunes, Serviço de Reumatologia - Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; 2Faculdade de Medicina - Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; 3Centro de Biotecnologia - Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

THU0076 SONIC HEDGEHOG PROMOTES SYNOWIAL HYPERPLASIA AND BONE DAMAGE THROUGH P38 MAPK SIGNALING IN EXPERIMENTAL ARTHRITIS

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Background: Abnormal activation of sonic hedgehog (SHH) signaling has been found in synovium from patients with rheumatoid arthritis (RA). Inhibition of SHH signaling is reported to attenuate inflammation and cartilage damage in adjuvant-induced arthritis (AIA). Previously we have demonstrated that SHH signaling promoted the tumor subset and a decrease in Trefoil factor-3 expressing cells, through p38 MAPK in vitro.

Objectives: In the current study, we aim to further explore the role of SHH-p38 MAPK signaling in regulating synovial hyperplasia and bone erosion in experimental arthritis.

Methods: Collagen-induced arthritis (CIA) mouse model was induced and the mice were injected with adenosine associated virus (AAV) overexpressing SHH or treated with small molecule inhibitors GDC-0449. SB203580 was administrated for the inhibition of p38 MAPK. The severity of paw inflammation was graded and serum levels of TNFα, IL-6 were detected. The histological features of arthritis were evaluated by H&E staining. The bone erosion was identified by micro-CT assessment and the number and function of osteoclasts were determined.

References:

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