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 inflammatory cytokines (1,2) - mechanisms that are important in the development and maintenance of several immunopathologies, as rheumatoid arthritis (RA) (3).

Objectives: To evaluate the therapeutic effect of recombinants cystatin 1 and cystatin 3 from Fasciola hepatica in a mouse 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 randomly divided into three groups: vehicle (n=9), treated with vehicle and phosphate-buffered saline), cystatin 1 (n=9, treated with 100 µg/dose of recombinant cystatin 1) and cystatin 3 (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 compared to vehicle (13.5±6.73) (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: 0.05±0.012ml, vehicle: 0.093±0.007ml) (p<0.05). Moreover, the treatment did not alter body weight (cystatin 3: 216.7±0.31g, vehicle: 210.5±0.38g) and spleen weight (cystatin 3: 7.04±0.31, vehicle: 7.16±0.38), as well as the T regulatory population (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: Mirian Farinon: None declared, Renata Ternus Pedo: None declared, Thales Hen De Rosa: None declared, Barbara Jonson Bartikoski: None declared, Thais Karnopp: None declared, Martim Cancela: None declared, Barbara Jonson Bartikoski: None declared, Thais Karnopp: None declared, Marilane B. Jonson: None declared, Renata T. Pedo: None declared, Thaís Karnopp: None declared, Martin Cancela: None declared, Henrique Bunselman Ferreira: None declared, Ricardo Xavier Consultant of: AbbVie, Pfizer, Novartis, Janssen, Eli Lilly, Roche DOI: 10.1136/annrheumdis-2020-eular.5097

THU0074 ANTI-ARTHRITIC EFFECT OF RECOMBINANT CYSTATIN 3 FROM FASCIOLA HEPATICA IN COLLAGEN-INDUCED ARTHRITIS

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Background: Jia et al. [2] found that recombinant Cystatin 3 from Fasciola hepatica prevented the development of collagen-induced arthritis (CIA) in mice. In a mouse model of CIA, Cystatin 3 (CST3) administration increased Treg cell subpopulation compared to control, with a decrease in IL-17 levels and Th17 cell number.

Objectives: To study the potential of recombinant cystatin 3 from Fasciola hepatica in an experimental model of CIA in mice.

Methods: C57BL/6 mice are immunized at day 0 and 14 with collagen type-II and Freund’s adjuvant at days 0 and 18. Animals were randomly divided into three groups: vehicle (n=9), treated with cystatin 3 (7.04±0.31g, vehicle: 2.7±0.32g) (p<0.05) and paw edema (cystatin 3: 0.05±0.012ml, vehicle: 0.093±0.007ml) (p<0.05). 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:

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THU0075 SONIC HEDGEHOG PROMOTES SYNOVIAL 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 Tregs responding to Treg depletion.

Objectives: 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 adenovirus associated virus (AAV) overexpressing SHH or treated with small molecule inhibitors GDC-0449. SB203580 was administered 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.

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THU0076 MIR-21 IN EXOMES DRIVEN FROM DENTAL PULP STEM CELLS AMELIORATE THE TREGS/TH17 IMMUNE RESPONSE VIA TARGETING STAT3 IN COLLAGEN-INDUCED ARTHRITIS MICE

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Background: Rheumatoid arthritis (RA) is a common and systemic autoimmune disease. Involvement of Tregs/Th17 may be responsible for the occurrence and development of RA. Dental pulp stem cells (DPSCs) can be a new therapeutic tool for immunological diseases. Treatment of Tregs/Th17 imbalance on the balance of Tregs/Th17 is still unclear.

Objectives: We explored the effect of exosomes derived from DPSCs on Tregs/Th17 balance.

Results: After DPSCs, Tregs increased and Th17 decreased. Moreover, the expression of Tregs cells increased in the spleen, changing the ratio of Tregs/Th17.

Conclusion: We elucidated the mechanism of the regulation of Tregs/Th17 balance by DPSCs-exo, that is, miR-21 in exosomes driven from dental pulp stem cells ameliorate the Tregs /Th17 immune response via targeting STAT3 in collagen-induced arthritis mice.