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SAT0360

BACTERIAL TRANSLOCATION IN THE ADJUVANT INDUCED ARTHRITIS MODEL: PRELIMINARY STUDY AND IMPACT OF NSAIDS

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Background: In patients with spondyloarthritis, the presence of intestinal inflammation and an increase in digestive permeability responsible for bacterial translocation has been described. No data are available on the effect of non-steroidal anti-inflammatory drugs (NSAIDs) on this bacterial translocation in patients with spondyloarthritis. Zonulin and lipopolysaccharide (LPS) have been described as good biomarkers of intestinal permeability and bacterial translocation, respectively. Adjuvant-induced arthritis (AIA) is a model of recent arthritis characterized by ossification and ankylosis in the post arthritis period. This model can be considered as a model of reactive arthritis in which our previous work has reported a clear efficacy of NSAIDs with differences between molecules at the structural and vascular levels.

Objectives: To test the hypothesis that there is an increase in digestive permeability and bacterial translocation in the AIA model and to show the influence of different NSAIDs on these two parameters.

Methods: Adjuvant-induced arthritis (AIA) was induced in 6-week-old male Lewis rats by an injection at the base of the tail of *Mycobacterium butyricum*. A group of non-AIA (control) rats received saline. At the first signs of arthritis, the AIA-rats were evaluated (arthritis score 0-6) and treated daily intraperitoneally with naproxen (10mg/kg/day), diclofenac (5mg/kg twice daily), celecoxib (3mg/kg/day) or saline solution (AIA-vehicle group). After 21 days of treatment, the rats were sacrificed and serum levels of zonulin and LPS were

evaluated by ELISA and liquid chromatography-mass spectrometry, respectively. Circulating levels of TNF- α and IL-1 β and paw radiographic score were measured.

Results: Compared to the control group, there was a significant increase in zonulin concentration ($p < 0.001$) in the AIA group. There was no significant difference in the concentration of LPS between the two groups. The levels of zonulin were correlated with the TNF- α levels ($R = -0.42$; $p = 0.032$) and the arthritis score ($R = 0.45$; $p = 0.013$) but not with the level of IL-1 β ($R =$; $p = 0.018$; $p = 0.39$). Treatment with NSAIDs significantly and equivalently decreased the arthritis score in each group. Compared to the vehicle group, treatment with naproxen significantly decreased the radiographic score ($p < 0.001$), TNF- α , IL-1 β ($p < 0.01$), zonulin ($p < 0.001$) and LPS ($p < 0.05$). Celecoxib decreased radiographic score ($p < 0.001$), IL-1 β ($p < 0.01$), TNF- α ($p < 0.01$) but increased zonulin levels ($p < 0.05$) without effect on LPS. Diclofenac also decreased radiographic score ($p < 0.001$), TNF- α ($p < 0.01$), and IL-1 β ($p < 0.01$) but increased both zonulin ($p < 0.01$) and LPS ($p < 0.001$).

Conclusion: We have demonstrated an increase in serum zonulin levels in the AIA model and a beneficial effect of naproxen on intestinal permeability and bacterial translocation in contrast to celecoxib and diclofenac. Moreover, the plasma zonulin levels were correlated with TNF- α supporting a pivotal role of TNF- α on the tight junctions in this model.

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SAT0361

HEALTHY HUMAN SPINAL PROCESSES PERI-ENTHESEAL T-CELLS EXHIBIT A TR1 RATHER THAN A FOXP3 REGULATORY PHENOTYPE

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Background: We have previously reported that the normal spinal enthesis has populations of conventional T-cells including CD4+ & CD8+ T-cells that could be induced to produce IL-17A and TNF following anti-CD3/CD28 stimulation. The biology of such cells in health including their normal function and antigen reactivity is completely unknown. The purpose of this work was to define the phenotype, functionality and TCR reactivity of such T-cells in health.

Figure 1. Transcriptional profiling of T-cells

Figure 2. TGF β from secretion enthesis T-cells

Objectives: To investigate whether the T-cells at the normal entheses were regulatory in nature and to determine the type of regulatory T-cell as Tr1 or FOXP3 regulatory T-cell and to determine T-cell reactivity.

Methods: Healthy interspinous ligament and spinous process with matched peripheral blood were harvested from patients undergoing elective spinal surgery (n=20). Enthesal soft tissue (EST) & peri-enthesal bone (PEB) was enzymatically digested and then sorted. Tr1 and Treg phenotypes were investigated using flow cytometry. Analysis of cytokines, growth factors and chemokines was performed by qRT-PCR, ELISA and flow cytometry. TCR sequencing was performed and a search for putative T-cell reactivity was done using TCR3 database.

Results: Pro-inflammatory cytokine transcripts including IL-17A, IL-17F, IL-22, IL-23 (p19) & TNF were very low or undetectable in the Enthesis T-cells (Fig 1). Flow cytometry confirmed enthesal T-cells had a Tr1 phenotype (CD4+ LAG3+ CD49b+). Intracellular flow cytometry showed enthesal T-cells had very low FOXP3 expression, when compared to their blood counterparts. Intracellular flow cytometry and gene expression showed high basal expression of growth factors and regulatory proteins such as IL-10 & TGF β , when compared to blood T-cells. RNA-Seq data, showed 13 potential TCR clonal sequences the most common of which are predicted to be reactive viral infection was CMV present in 8 sequences and Influenza A virus present in 2 sequences.

Conclusion: The healthy human entheses has regulatory T-cells of a Tr1 phenotype rather than a FOXP3 Treg phenotype. Many clones have antigen specificity indicating reactivity to prior infection. These findings suggest that conventional enthesal T-cells have a role in entheses immune homeostasis.

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SAT0362

ASSOCIATION OF GUT DYSBIOSIS WITH STRUCTURAL DAMAGE AND ACTIVITY IN AXIAL SPONDYLOARTHRITIS PATIENTS. DATA FROM THE COSPAR REGISTRY.

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Background: The etiopathogenesis of axial spondyloarthritis (AxSpA) is multifactorial. The possible role of alteration in gut microbiome (dysbiosis) has been recently suggested. However, the association of dysbiosis with structural damage is still unknown and further studies are needed to assess its association with disease activity.

Objectives: To determine the alterations in the gut microbiota in AxSpA patients. To evaluate whether changes in the gut microbiota in AxSpA patients are associated with structural damage or disease activity.

Methods: Fifteen AxSpA patients and 15 healthy donors (HDs) were included in a cross-sectional study. Disease activity variables such as C-reactive protein and ESR were measured. Structural damage was determined by lateral X-rays of the cervical and lumbar spine to establish the mSASSS index. Axial mobility was evaluated using the BASMI index and the entheses affection was evaluated using ultrasound to obtain the MASEI index. Gut microbiota was measured using the Ion Torrent S5 platform and sequences were processed using the QIIME2. Chi-square and Mann-Whitney U were used, and correlations were determined using the Spearman Rho test. Significant differences were considered p < 0.05.

Results: Alpha diversity indicators, such as the number of observed OTUs group and the faith index, showed a greater richness in AxSpA compared to HDs (p=0.03 and p=0.01). A significant decrease in family Bacteroidaceae (p=0.006) and an increase in families Synergistaceae and Bifidobacteriaceae were found

in the microbiota of AxSpA (p=0.036, p=0.049). According to genera, Bacteroides decreased in AxSpA (p=0.006), while Dialister and Bifidobacterium increased (p=0.010 and p=0.046). Positive correlation among lumbar mSASSS (r=0.508, p=0.019) and Synergistaceae was found. This family was also increased along with the increase in entheses damage (MASEI index (r=0.656, p=0.028)) and axial mobility by the BASMI index (r=0.529, p=0.011). Correlation studies between the decrease in Bacteroidaceae and Bacteroides with disease activity measured by ASDAS (r=-0.697, p=0.025; r=-0.770, p=0.009) was also significant. Positive correlation was observed between Dialister with mSASSS (r=0.549, p=0.010) and BASMI (r=0.512, p=0.015).

Conclusion: 1) AxSpA patients had a significant alteration of the gut microbiota. 2) These alterations are associated with radiographic damage, disease activity, affection of entheses and axial mobility.

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SAT0363

DELPHINIDIN DOSE-DEPENDENTLY DIMINISHES PERIPHERAL IL-17 AND IFN- γ PRODUCING LYMPHOCYTES IN PSORIATIC ARTHRITIS

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Background: Delphinidin, a dietary anthocyanidin and powerful anti-oxidant from pigmented fruits and vegetables, has broad anti-inflammatory properties. In a human skin model of psoriasis, delphinidin reduced expression of proliferative and inflammatory markers (1).

Objectives: The rationale of our study was to assess whether delphinidin can in vitro suppress IL-17 and IFN- γ production in peripheral blood mononuclear cell (PBMC) subsets from patients with psoriatic arthritis (PsA).

Methods: PBMCs were obtained from 24 patients with PsA attending the outpatient clinic of the Department of Rheumatology/clinical Immunology at the University General Hospital of Larissa, Greece. 16 age- and sex-matched healthy volunteers were also included in the study. Delphinidin was supplemented at a concentration ranging from 1 to 50 μ g/ml, one hour prior to cell stimulation. Cell viability (Annexin V staining) and innate/adaptive lymphocyte subpopulations were assessed by flow cytometry with a panel of fluorochrome-conjugated antibodies against CD56, CD3, CD4 and CD8. Intracellular expression of IL-17 and IFN- γ was measured following PMA/ionomycin stimulation for 5 hours using standard cell permeabilization protocols and monoclonal antibodies against IL-17 and IFN- γ .

Results: Delphinidin at concentration ≥ 10 μ g/ml sharply diminished IL-17-production by CD4(+) T cells (Th17) and CD56(+)CD3(+) (NKT) cells from patients with psoriatic arthritis and normal controls (p $\leq$ 0.05). IFN- γ producing T (CD4 and CD8) cells, as well as NK and NKT cells were also dose-dependently suppressed following delphinidin pre-incubation in both patients and healthy controls. Inhibition of IFN- γ (+) cells ranged from 27 to 69% and peaked at delphinidin concentration 20-50 μ g/ml. The inhibitory effect of delphinidin on IL-17 and IFN- γ producing lymphocytes was not due to compromised cell viability, as assessed by annexin V binding.

Conclusion: Delphinidin exerts, in a dose-dependent manner, a profound in vitro inhibitory effect on T cell and NKT cell IL-17 and IFN- γ production in PsA, and therefore, it may be used as a dietary immunosuppressant, complementary to standard treatment.

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