for the development of ROA up to 10 years later. Future directions include developing a predictive model that incorporates multiple features.

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Different pathophysiological pathways in axial and peripheral disease: Peripheral and axial spondyloarthritis: to split or to lump?

OP0199

THE HUMAN ENTHESIS HARBOURS RESIDENT ADAPTIVE CD4+ AND CD8+ T-CELLS WITH INDUCIBLE IL-17A AND TNF PROTEIN THAT IS PHARMACOLOGICALLY SUPPRESSED BY RORγT AND PDE4 INHIBITORS BUT NOT METHOTREXATE IN A NOVEL IN VITRO ENTHESITIS MODEL

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Background: Animal models have demonstrated that enthesitis is the primary lesion in experimental spondyloarthritis (SpA). In mice, innate lymphocytes were suggested as the major cytokine producers at the enthesis.

Objectives: We tested the hypothesis that the human enthesis harbours tissue resident conventional T-cells. We also assessed their ability to express SpA-related cytokines including TNF and IL-17A and if this could be blocked using psoriasis therapeutic agents (methotrexate (MTX), and phosphodiesterase type 4 inhibitor (PDE4i)) and experimental RORγt inhibitors (RORγti).

Methods: Entheseal spinous process was obtained from patients undergoing elective orthopedic procedures (n=20) and mechanically digested or processed for confocal staining and flow cytometry. CD4+ and CD8+ T-cells were sorted and RNA was isolated and analysed by qPCR. Magnetically isolated cells were stimulated using an anti-CD3/CD2/CD28 bead with and without the presence of MTX, RORγti and PDE4i. Following stimulation IL-17A and TNF were measured by ELISA and intracellular flow cytometry.

Results: CD4+ and CD8+ T-cells represent 35.7% and 23.7% of T-cells in the enthesis, respectively, with topographic confirmation by anti-CD3 immunofluorescence staining. Entheseal tissue contained a higher proportion of CD4+ and CD8 + T-cells expressing a resident memory phenotype (CD69+/CD45RA-) compared to matched blood. Sorted T-cells from entheseal tissue had a gene expression profile consistent with a tissue resident phenotype and CD4+ and CD8+ T-cells showed increased expression immunomodulatory genes including IL-10 and TGF-β compared to peripheral blood T-cells ($p<0.001$). Following stimulation CD4 + T-cells produced more TNF than CD8+ T-cells ($p<0.05$), IL-17A was robustly detected in CD4+ but not CD8+ T-cells. TNF and IL-17A production from CD4+ T-cells was effectively inhibited by PDE4i ($p<0.05$), while RORγti only reduced IL-17 secretion ($p<0.001$). MTX had no significant impact on both TNF and IL-17A production in either cell population. This pattern of inhibition was mirrored in TNF secretion from CD8+ T-cells.

Conclusion: This is the first description of conventional CD4+ and CD8+ enthesis resident T-cells. PDE4i was effective in abrogating induced TNF production and IL-17, whereas RORγti is highly effective for IL-17A production but not TNF. In contrast, MTX had little effect on *in vitro* enthesitis model cytokine production. These findings may have some practical implications in the treatment of subclinical enthesitis.

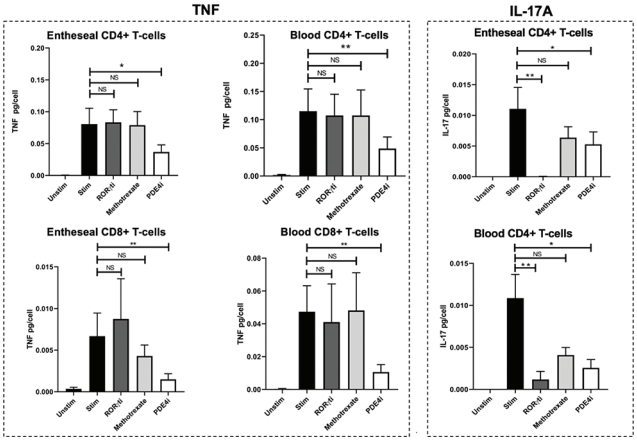
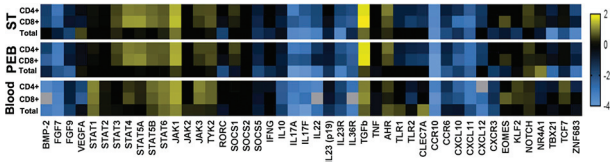


Figure 1. Effect of different therapeutic agents on the TNF and IL-17A production by resident entheseasl T -cells and matched peripheral blood

Figure 2. Gene expression profile of entheseal T-cells (soft tissue and adjacent bone) compared to peripheral blood



Abbreviations: ST, entheseal soft tissue; PEB, peri-entheseal bone.

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OP0200

A SET OF INFLAMMATORY MARKERS ALLOWING TO DETECT SYSTEMIC INFLAMMATION IN PSORIATIC SKIN, ENTHESEAL AND JOINT DISEASE IN THE ABSENCE OF CRP AND THEIR LINK TO CLINICAL DISEASE MANIFESTATION

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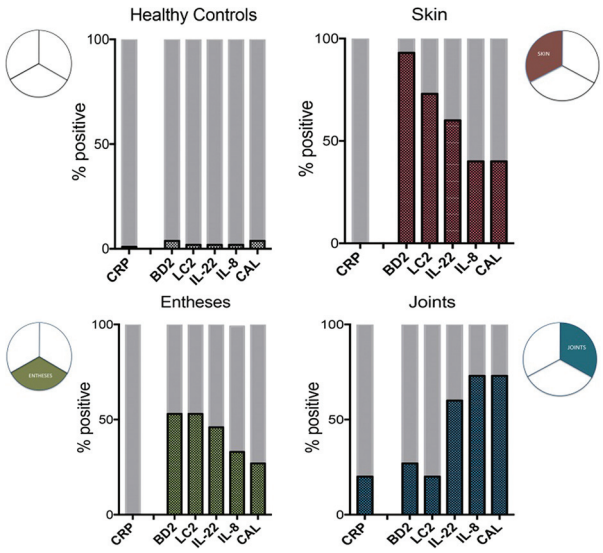
Background: Psoriatic disease is composed of skin, entheseal and joint disease, which can manifest isolated or combined. Little is known about the systemic inflammation levels in psoriatic disease as a robust IL-6 signal is missing and therefore acute phase reactants such as C-reactive protein are often normal. Measuring systemic inflammation in the different manifestations of psoriatic disease is therefore a continuous unmet need.

Objectives: To better define systemic inflammation in patients with psoriatic disease limited to the skin (S), the entheses (E) or the joints (arthritis, A) or with a combination of these disease manifestations (SE, SA, EA, SEA).

Methods: Hypothesis-driven approach selecting markers that are (i) either targets of IL-23/IL-17 pathway activation (b-defensin 2, lipocalin 2, IL-22), (ii) associated with neutrophil/monocyte activation (calprotectin, IL-8) and (iii) achieve serum concentrations sufficient for reliable detection by standard ELISA. Parameters were assessed in 210 individuals comprising 105 healthy controls and 105 patients with psoriatic disease (each 15 for isolated (S, E, A) and composed disease manifestations SE, SA, EA, SEA). Results are expressed as percent positive patients with levels above three standard deviations over the mean level in healthy controls. In addition, 6-months sequential data on levels of these markers were collected in 20 patients treated with secukinumab or adalimumab to test treatment effects.

Results: CRP levels were normal in the majority of individuals. The respective percentages of patients with normal CRP (<5mg/L) were as follows: S: 100%, E: 100%, A: 80%, SE: 93%, SA: 67%, EA: 73%, SEA: 67% (Figure). Thus, CRP is only elevated in a subset of patients with arthritis. In sharp contrast, beta-defensin 2 levels (>1.88 ng/mL) and lipocalin-2 (>24.7 ng/mL) were elevated in the majority of patients with isolated skin and entheseal, but not joint disease. Conversely, elevations of calprotectin (>3.58 mig/mL) and IL-8 (>10.3 pg/mL) were found in the majority of patients with isolated joint disease. IL-22 was elevated (>17.1 pg/mL) in all three manifestations of psoriatic disease. Reflecting a combination of the findings the vast majority of patients with composed disease manifestation (SE, SA, EA, SEA) showed widespread marker elevation. IL-17 and TNF inhibition differentially lowered and partially normalized elevated markers of inflammation.



Conclusion: Systemic inflammation is detectable in the majority of patients with psoriatic disease, even if CRP is normal. The respective marker pattern depends on the manifestation (skin, entheses, joints) of psoriatic disease, with beta-defensin 2 and lipocalin-2 reflecting skin and entheseal disease, calprotectin and IL-8 joint disease and IL-22 a combination of these disease manifestations.

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My joints hurt and I'm overwhelmingly tired – fatigue in rheumatoid arthritis

OP0201 FATIGUE IN JUVENILE IDIOPATIC ARTHRITIS AFTER 18 YEARS OF FOLLOW-UP

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Background: Fatigue is common in adults with rheumatic disease and has also been shown in adolescents with juvenile idiopathic arthritis (JIA). Knowledge on fatigue in JIA in long-term follow-up is limited.

Objectives: To study the prevalence and severity of fatigue 18 years after onset of JIA.

Methods: In this close to population-based cohort study from defined geographical areas of Norway, Sweden, Denmark and Finland, consecutive cases of JIA with disease onset in 1997 to 2000 were prospectively enrolled (1). At 18-year follow-up, fatigue was measured using Fatigue Severity Scale (FSS, range 0-7) (2), and severe fatigue was defined as FSS $\geq$4. General health status was measured with Health Assessment Questionnaire (HAQ) and 36-Item Short Form Health Survey (SF-36). Reduced health was defined as HAQ >0, and SF-36 <40 (according to the physical component summary score/mental component summary score (PCS/MCS)). Pain was measured with 10 cm visual analogue scale (VAS), 0 = no pain, >0 = pain. Remission was defined according to the preliminary criteria described by Wallace. A Norwegian healthy cohort was used for comparison. Multivariable logistic regression analyses were performed.

Results: Among 434 eligible JIA participants 377 completed a Fatigue Severity Scale (FSS) measurement at the 18-year follow-up and were included. Of these 72% were girls, 53% had oligoarticular disease six months after onset, median age at onset was 5.6 (IQR 2.6-9.7) years, and age at the 18-year visit was 23.1 (IQR 20.3-27.2). Mean total FSS (±SD) was 3.2 (±1.5), and participants with active disease scored 3.6 (±1.6) compared to 2.9 (±1.4) for those in remission off medication. The highest total FSS was found in those with SF-36 PCS and/or MCS <40 (4.7 (±1.6) and 4.6 (±1.6), respectively). Severe fatigue was considerably more frequent in participants with active disease (36%, odds ratio (OR) 2.5) compared to those in remission off medication (19%), HAQ score >0 (47%, OR 4.1) compared to HAQ score =0 (18%), SF-36 PCS/MCS <40 (64/61%, OR 7.1/6.9) compared to SF-36 PCS/MCS $\geq$40 (20/19%), and VAS pain >0 (36%, OR 3.8) compared to VAS pain =0 (13%). The proportion of severe fatigue in a healthy Norwegian control cohort was 12%.

Conclusion: At 18-year follow-up fatigue was a prominent symptom in JIA, and we found consistently higher fatigue burden and considerably more severe fatigue among participants with active disease, pain and self-reported health problems, compared to those without. We suggest fatigue to be measured at long-term follow-up both in clinical and research settings.

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