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0015

IL-17 BLOCKADE WITH SECUKINUMAB IN PERIPHERAL SPONDYLOARTHRITIS IMPACTS SYNOVIAL IMMUNOPATHOLOGY WITHOUT COMPROMISING SYSTEMIC IMMUNE RESPONSES

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Introduction Secukinumab (anti-IL-17A) is an effective therapy for ankylosing spondylitis (AS) and psoriatic arthritis (PsA), the prototypical forms of spondyloarthritis (SpA).

Objectives This study assessed if secukinumab modulates the immunopathology of target lesions without blunting systemic immune responses, using peripheral SpA (pSpA) as model.

Methods 20 active peripheral SpA patients were included in a 12 week open-label trial with secukinumab (300 mg weekly for 4 weeks followed by every 4 weeks). Outcomes included clinical response, cytokine production by peripheral blood cells using TruCulture technology, and histological and qPCR analysis of synovial biopsies before and after treatment.

Results All patients completed the 12 week study, without SAEs or severe treatment-related AEs. The primary efficacy endpoint, EULAR DAS 28 response at wk 12, was achieved by 18/20 patients (10 good and 8 moderate responders), with rapid and significant improvements in all clinical disease activity measurements. Clinical improvement in joint counts was associated with histological decrease in synovial sublining macrophages ($p=0.028$) and neutrophils ($p=0.004$), sensitive synovial biomarkers of response in pSpA, as well as with decreased synovial expression of IL-17A ($p=0.010$) but not TNF. Systemically, secukinumab treatment decreased CRP ($p<0.01$) and ESR ($p<0.01$), as well as MMP-3 production in the triculture system ($p<0.01$). With exception of IL-17A itself, however, the capacity of peripheral blood cells to produce a broad panel of cytokines and chemokines upon stimulation with microbial antigens was not affected.

Conclusions This mechanism-of-action study in pSpA indicates that clinical improvement upon secukinumab treatment is paralleled by immunomodulation of the inflamed target tissues without compromising systemic immune responses.

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0016

SYNOVIAL IL-17+ CD8+ T CELLS ARE A PRO-INFLAMMATORY TISSUE RESIDENT POPULATION ENRICHED IN SPONDYLOARTHRITIS

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Introduction Spondyloarthritis (SpA) describes a group of inflammatory joint diseases affecting ~1% of the population. SpA has strong genetic associations with HLA-B/RUNX3 implying a role for CD8 +T cells. Furthermore, genetic associations with IL23R/TRAF3IP2 and the clinical efficacy of IL-17 blockade in SpA, indicate a role for IL-17 in these diseases.

Objectives This provides a strong rationale to investigate the presence, phenotype and functional capacity of IL-17 +CD8 +T cells in the joints of patients with SpA.

Methods Mononuclear cells were isolated from peripheral blood (PB) and synovial fluid (SF) from patients with PsA, other peripheral-SpA types (including ankylosing spondylitis/non-radiographic axial SpA/reactive arthritis/enteropathic arthritis/undifferentiated SpA) and rheumatoid arthritis (RA). Cells were stimulated *ex-vivo* before analysis of surface marker/cytotoxic molecule/cytokine expression by flow cytometry or cytokine secretion assay (CSA). Sorting was performed on unstimulated SFMC and gene expression analysis performed by RT-PCR.

Results Frequencies of IL-17 +CD8+T cells were increased in the SF of PsA ($p<0.0001$) and SpA ($p=0.0009$), but not RA patients ($p=0.3$) vs. paired PB, with IL-17 secretion confirmed by CSA. Phenotypically, SF IL-17 +CD8+T cells were largely composed of TCRab +T cells (~95%), with small proportions of MAIT/NK/gd-T-cells (all <5%). Considerable proportions of SF IL-17 +CD8+T cells expressed markers typical of skin/gut tissue residency including $\beta 7$ integrin (median-66%), CD49a (57%), and cutaneous lymphocyte antigen (27%), as well as Th17-associated markers (CCR6/CD161 expression). Interestingly, SF IL-17 +CD8+T cells expressed hallmarks of tissue resident memory T cells (T_{RM} ; CD45RA-CCR7-CD103+) whilst sorted CD8 +CD69+CD103+ T_{RM} cells from the PsA joint were enriched for IL-17, and expressed RORC transcript. Functionally, a high frequency of SF IL-17 +CD8+T cells co-expressed granzyme B and the pro-inflammatory cytokines IFN- γ , GM-CSF, TNF- α , some IL-21 and IL-22, but very little anti-inflammatory IL-10.

Conclusions These novel findings show an enrichment of IL-17 +CD8+T cells in the joints of patients across multiple SpA types and identify a phenotypic signature for IL-17 +CD8+T cells, consisting of type 17 and tissue-associated markers. Our data demonstrate, to our best knowledge for the first time, the presence of T_{RM} cells in the PsA joint. Functionally, IL-17 +CD8+T cells exhibit cytotoxic potential and co-express pro-inflammatory cytokines, suggesting these cells are important contributors to the pathogenesis of PsA and other SpA.

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0017

IL-7 IN PRIMARY SJÖGREN SYNDROME (PSS) IS SECRETED BY SALIVARY GLAND EPITHELIAL CELLS AFTER IFN STIMULATION AND IS ASSOCIATED WITH B-CELL ACTIVATION

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Introduction pSS is characterised by a strong IFN signature, ectopic germinal centres formation and a chronic blood lymphopenia. IL-7 plays a central part in T cells homeostasis and in lymphoid structures organisation.

Objectives To assess the role of IL-7 in pSS pathogenesis.

Methods IL-7 serum level was assessed in 372 pSS patients and 73 paired controls. Primary cultures of salivary gland epithelial cells (SGEC) from patients and controls were stimulated by Poly I:C 30 ng/ml, IFN- α 600 UI/ml, IFN- γ 5 ng/ml and IFN- λ (IL-28) 25 ng/ml for 72 hours. IL-7 secretion was tested in culture supernatant by ELISA. IL-7 expression after 24 hours stimulation was assessed by quantitative RT-PCR. IL-7 and its receptor's expressions were evaluated in RNA-Seq analysis from cells from salivary glands biopsies (SGB) and PBMC.

Results pSS patients had higher serum IL-7 levels than controls: 7.56 ng/ml $\pm$ 8.52 (mean $\pm$ SD) versus 4.86 ng/ml $\pm$ 5.59; $p < 0.0001$. A positive correlation with B cells activation markers, IFN-induced chemokines and disease activity markers was observed. In multivariate analysis, serum IL-7 level was associated with CXCL13, anti-SSA, RF, κ light-chain and low C4.

SGEC stimulation with Poly I:C, IFN- α , - γ and - λ induced IL-7 protein secretion in the supernatant ($p = 0.002$, $p = 0.004$, $p = 0.007$, $p = 0.004$ respectively). A trend for a greater IL-7 production in pSS patients compared to controls was observed. IL-7 expression was confirmed by quantitative RT-PCR. Among cell subsets purified *ex vivo* from SGB and PBMC, RNA-Seq analysis showed a greater expression of IL-7 by epithelial cells of patients compared to controls ($p = 0.03$). No difference was observed regarding T and B cells either from biopsies or PBMC. IL-7 receptor expression was equivalent between patients and controls. Analysis of T cells exhaustion profile and IL-7 intracellular signalling are on-going.

Conclusions Our data demonstrate that IL-7 is secreted within the target tissue of pSS by SGEC after stimulation by IFNs. This IFN/IL-7 pathway can be involved in the organisation of ectopic germinal centres found in pSS. But more importantly, since IL-7 is one of the major controller of homeostasis of T cells, this IFN/IL-7 pathway could be involved in the persistent lymphopenia which is a hallmark of the disease, either by favouring exhaustion of T cells or by an impaired function of

the IL-7 intracellular signalling. Both mechanisms are currently explored and will be presented.

Disclosure of interest None declared

0018

CCR6+ T HELPER CELLS DRIVE ANTIGEN-INDUCED ARTHRITIS VIA THE IL-23R PATHWAY

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Introduction The IL-23/IL-17A immune pathway is important for the progression of T cell-mediated arthritis. However, it is not known where IL-23R⁺ T cells locate at different stages of arthritis and which IL-23R⁺ cells are drivers of joint inflammation.

Objectives We aimed to identify IL-23R⁺ T cells in the secondary lymphoid organs and synovium during the development and progression of antigen-induced arthritis (AIA). Furthermore, we studied which IL-23R⁺ cells drive full-blown AIA.

Methods To induce AIA, IL-23R^{+/+} (wild type), heterozygous IL-23R^{+/-}/GFP (IL-23R-GFPKI reporter), and IL-23R^{GFP/GFP} (IL-23RKO) mice were immunised with methylated bovine serum albumin (mBSA) in Complete Freund's Adjuvant. After 7 days mice were injected in the knee joints with mBSA. Mice were macroscopically scored and knees were used for histological analysis of inflammation and bone erosion. The spleen, inguinal and popliteal lymph nodes, and the synovium were collected and assessed for expression of GFP/IL-23R⁺ cells. Adoptive transfer of CCR6⁺ T helper cells and $\gamma\delta$ T cells from heterozygous mice into IL-23RKO mice was performed via i.v. injection prior to AIA induction.

Results AIA disease progression was mainly driven by the IL-23R pathway as IL-23RKO mice had significantly lower arthritis scores and less bone damage. Heterozygous mice had similar disease scores to WT mice, indicating that half of the receptor expression is sufficient to drive disease. Flow cytometric analysis of GFP/IL-23R expression revealed that among the T cells, CCR6⁺ T helper and $\gamma\delta$ T cells but not CD8⁺ T cells expressed the IL-23R in the lymphoid tissues. During the progressive phase of arthritis, lymphoid tissue cell numbers were lower in IL-23RKO mice. On the other hand, the overall percentage of T cells was higher in the IL-23RKO lymphoid tissues, suggesting that these cells develop but remain in the lymphoid tissues. CD4⁺ and $\gamma\delta$ T cells but not CD8⁺ T cells were abundantly present in the WT joints during arthritis, but decreased in IL-23RKO joints. Adoptive transfer of CCR6⁺ T helper and $\gamma\delta$ T cells into IL-23RKO mice revealed that CCR6⁺ T helper cells are the main drivers of AIA.

Conclusions AIA progression is driven by IL-23R signalling and CCR6⁺ T helper cells can rescue arthritis in IL-23R deficient mice. Among the T cells, only CCR6⁺ T helper and $\gamma\delta$ T cells express the IL-23R in the lymphoid tissues. IL23R signalling might be involved in T cell proliferation and/or migration, since CD4⁺ and $\gamma\delta$ T cell infiltration is decreased in the IL-23RKO synovium.

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