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P061 TARGETING B-CELL ACTIVATING FACTOR (BAFF) IMPAIRS ECTOPIC LYMPHONEOGENESIS IN MURINE MODELS OF SJÖGREN'S SYNDROME

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Introduction Tertiary lymphoid structures (TLS) characterised by germinal centre formation and B cell proliferation represent the histological hallmark of primary Sjögren's syndrome (pSS). However, the events preceding the formation of such ectopic structures and factors driving their persistence are unknown. Overexpression of BAFF, also known as B cell lymphocyte stimulator (BLyS), in pSS patients has been linked with the presence of autoreactive B cells and autoantibody production.¹ Furthermore, in pSS salivary glands BAFF is associated with the expansion of specific B cell subsets, and with B cell repopulation post rituximab treatment.²

Objectives In this work we aimed to dissect the dynamics of B cell subsets within tertiary lymphoid structures following BAFF-targeted treatment in both inducible and chronic animal models that mimic the histological features of pSS.

Methods Submandibular salivary glands of C57BL/6 mice were intra-ductally cannulated with luciferase-encoding replication-deficient adenovirus to induce TLS formation as previously described.³ Prior to salivary gland cannulation, mice were treated with two doses (i.p.) of either anti-BLyS mAb or isotype control. Salivary glands were dissected at day 15 post-cannulation and TLS formation in both groups was assessed. NOD.B10.H2b mice were similarly treated with anti-BLyS mAb at 26 weeks old and salivary gland infiltrates assessed 21 days later.

Results Histological analysis of salivary glands from anti-BLyS treated C57BL/6 animals unveiled severely compromised TLS formation. Post anti-BLyS treatment, salivary glands were infiltrated by T cell clusters but only few, and scattered, B cells were present, contrasting with fully developed and organised TLS in the salivary glands of mice treated with isotype control. Significantly lower numbers of B cells, particularly from the B2 subset, as well as plasmablasts, infiltrated salivary glands of anti-BLyS treated mice. However, treatment with anti-BLyS did not affect numbers of infiltrating T cells (both CD4 and CD8), proliferative T cells, or plasma cells in inflamed salivary glands. In a chronic setting, salivary glands from NOD.B10.H2b mice were also infiltrated by significantly lower numbers of B2 B cells following anti-BLyS treatment.

Conclusions Our data highlights BAFF as a key player in ectopic lymphoneogenesis during inflammation as well as a subset-specific role for BAFF in B cell maturation. Furthermore, these results support future studies of BAFF-targeted therapeutics in pSS.

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P062 SIGNIFICANT DECREASE OF T-CELLS BUT NOT MACROPHAGES IN THE SYNOVIUM OF PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS AFTER TREATMENT WITH TOCILIZUMAB

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Introduction Tocilizumab (TCZ) is an anti-IL6R monoclonal antibody approved for the treatment of Rheumatoid Arthritis (RA). There is limited data on synovial tissue histology changes.

Objectives The aim of this study was to evaluate the effect of TCZ on synovial cell populations and on citrullination.

Methods 15 patients with definite RA, according to ACR 1987 criteria, independent of disease duration, were included. Synovial biopsies were obtained before and after 8 weeks of treatment with TCZ from all patients. We evaluated by immunohistochemistry (IHC) expression of citrullinated proteins (CP) and protein arginine deiminase (PAD) enzymes in synovial tissue before and after treatment with TCZ (1325:C03, 1325:B09, PAD2, PAD4). Negative controls were used for each antibody. Expression of CD68, CD3, CD20 and CD55 was also evaluated. Evaluation of all IHC variables was performed by two blinded independent observers using a semi-quantitative score on a 0–3 scale (0, no staining; 1, low amounts of staining; 2, moderate amounts of staining; 3, high amounts of staining). Paired-wised Wilcoxon Signed Ranks Test was used to compare the median value before and after treatment.

Abstract P062 Table 1

	Baseline	12 weeks	Wilcoxon signed ranks test
DAS28 BL	5.9 (4.7–6.8)	2.98 (2.0–3.8)	0.028
SJC BL	9 (3–14)	1 (0–4.25)	0.009
TJC BL	10 (4–15)	1 (0–2.25)	0.017
ESR BL	34 (15–69)	6 (5–16)	0.001
CRP BL	11 (5–27)	1 (1–2)	0.005
CD68	2 (1–3)	2 (0.75–3)	0.41
CD3	2 (1–3)	1 (0–2)	0.046
CD55	2 (2–3)	1.5 (1–2)	0.05
C03 (cit)	1 (0–1)	0 (0–1)	0.025
B09 (cit)	2 (1–2)	2 (1–2)	0.20
PAD2	3 (2–3)	2 (1.5–3)	0.16
PAD4	2 (2–3)	2 (2–3)	0.37

Results The median (IQR) age, disease duration, N. prior biologic DMARDs and DAS28 at baseline was 66 (58–79), 4 (1–13), 1 (0–2), 6 (5–7), respectively. 93% were female, 53% were RF + and 60% ACPA+, 53% had concomitant glucocorticoids and only 27% had concomitant conventional synthetic DMARDs. Significant reductions in DAS28, swollen and

tender joint count (SJC and TJC, respectively), and acute phase reactants (ESR and CRP) were observed between baseline and 8 weeks (table 1). By IHC, TCZ induced significant decrease in the number of CD3, CD3 and CD55, but not in the number of the other CP, PAD2, PAD4 and CD68 (table 1). No significant correlations between reduction in disease activity (by Δ DAS28, Δ SJC, Δ TJC, Δ ESR, Δ CRP) and reduction in CP, CD68 or CD3 were found.

Conclusions Treatment with IL6R blockade reduced the number of synovial tissue T cells. This was observed in the responders but not in non-responders. Significant reduction in citrullination as assessed by expression of 1325:C03 but not 1325:B09. No significant reduction in macrophages was observed.

Disclosure of interest None declared

P063

EFFECT OF ADIPOKINES AND IL-17 ON SYNOVIAL FIBROBLAST FROM DIFFERENT RHEUMATIC DISEASE BACKGROUNDS

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Introduction Rheumatoid arthritis (RA) and psoriatic arthritis (PsA) have several features in common but also possess distinct differences. Synovial fibroblasts (SF) are known key effector cells in the pathophysiology of RA. We hypothesised that differential responses of SF from patients with PsA and RA to various stimuli including adipokines and cytokines may contribute to those differences. For example, IL-17 (also found in synovial tissue) is of particular therapeutic significance in PsA but not as effective in RA. Thus far, IL-17 in its isoform IL-17A has been the major therapeutic target in PsA but IL-17F also plays a role in the IL-23/IL-17 axis of inflammatory diseases.

Objectives Therefore, we analysed the responses of SF from patients with PsA, RA or no rheumatic disease to IL-17A/F $\pm$ TNF- α and selected adipokines.

Methods SF were isolated from patients with PsA, RA or non-rheumatic disease controls (N), each undergoing joint surgery. PsASF, RASF and NSF were stimulated with recombinant IL-17A/F, TNF-, visfatin, and resistin. A neutralising anti-IL-17A antibody was used to verify specificity of the IL-17A effects. Secretion of the proinflammatory cytokine IL-6 was used as the initial readout parameter and was quantified using a commercial immunoassay.

Results Stimulation with visfatin caused a strong increase in IL-6 secretion in all SF types (n=3 each), while resistin had no effect. Differences in responses were not statistically significant between the SF types studied. IL-17A at concentrations found in serum or synovial fluid did not induce IL-6 secretion in any of the SF. Dose-response curve analysis showed that considerably higher concentrations of IL-17A, which may occur locally in tissue, are required for the induction of IL-6 secretion. An anti-IL-17A antibody abolished the effect, thus showing that the effect is specific for IL-17A. The effects of IL-17A and IL-17F on IL-6 secretion by PsASF could be strongly amplified by a co-stimulation with TNF- α (IL-17A:

5-fold vs 113-fold; IL-17F: 1.7-fold vs 39-fold; TNF- α alone: 12-fold). The effects were stronger for IL-17A than for IL-17F with or without TNF co-stimulation. No effect of IL-17F alone was observed on NSF (n=1).

Conclusions SF from RA and PsA were not differentially affected by the adipokines visfatin and resistin or IL-17A when used at serum or synovial fluid concentrations. The property of IL-17F not affecting NSF but PsASF (and RASF) may be beneficial in its use as therapeutic target.

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P064

ADIPOSE TISSUES OBTAINED FROM RA AND OA PATIENTS DIFFER IN CYTOKINE AND CHEMOKINE SECRETION

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Introduction Rheumatoid arthritis (RA) and osteoarthritis (OA) lead to joint destruction and disability. Although both diseases are characterised by inflammation of the joints as well as systemic inflammation, their pathogenesis is different. Despite the progress in the treatment both diseases are still incurable. Articular adipose tissue (AAT) and subcutaneous adipose tissue (ScAT) are supposed to contribute to joint and systemic inflammation, respectively. Our previous work showed that AAT from RA patients synthesises factors relevant to disease pathogenesis and/or progression and this secretion is usually higher from articular than subcutaneous adipose tissue.^{1,2}

Objectives The aims of present work were (i) to investigate whether AAT obtained from OA patients is also more active than ScAT and (ii) to compare secretory activity of adipose tissues from RA and OA patients.

Methods AAT and ScAT explants obtained from OA [(n=44; female (F)/male (M)=36/8; age=62 (mean) (35–71) (min-max)] and RA (n=43; F/M=35/8; age=54 (31–70)] patients during knee joint replacement surgery were cultured (100 mg/ml) for 24 hours in DMEM. Concentrations of proinflammatory (IL-6, TNF), anti-inflammatory (IL-1Ra, IL-10, TGF β) cytokines, chemokines (CCL2, CCL5) and metalloproteinase MMP-3 was measured in culture supernatants by ELISA.

Results In both diseases AAT secreted spontaneously more IL-1Ra, TGF β and MMP-3 than ScAT while the release of other factors was minute (TNF, IL-10, CCL5) or moderate (CCL2) and did not differ between tissues. The only exception was IL-6 produced in larger quantity by AAT than ScAT from OA patients. Both adipose tissues from OA patients released significantly more TNF, IL-1Ra and CCL2 than tissues from RA patients. Moreover, AAT from OA produced more MMP-3 than respective tissue of RA patients while rheumatoid ScAT secreted more TGF β . We did not find differences in basal secretion of IL-6, IL-10 and CCL5 between diseases.

Conclusions Despite the fact, that similarly to RA the secretion of cytokines and chemokines in OA was usually higher in AAT than in ScAT, also the latter tissue released considerable quantity of tested factors and thus may contribute to systemic inflammation. Unexpectedly, our results give also evidence that basal secretory activity of adipose tissues from OA patients is usually higher than from RA patients. It is possibly caused by