similarly effective in abolishing the synergistic effect of IL-17A + TNF- α in RASF and PsASF.

Conclusion: According to our data, the differences in the therapeutic effectiveness of the anti-IL17A biologic secukinumab cannot be attributed to differential SF responses since the response to IL-17A alone and IL-17A together with TNF- α is not stronger for PsASF than for RASF and since secukinumab was similarly effective for both SF types. Furthermore, in a proinflammatory milieu with increased TNF levels, both IL-17A and IL-17F can contribute to promoting inflammation in the pathophysiology of PsA and RA.

Acknowledgement: Supported by an unrestricted educational grant from Celgene GmbH.

Disclosure of Interests: Klaus Frommer: None declared, Stefan Rehart: None declared, Ulf Müller-Ladner Grant/research support from: Projekt supported by an unrestricted educational grant from Celgene GmbH., Elena Neumann: None declared

DOI: 10.1136/annrheumdis-2019-eular.3321

THU0029 FAS LIGAND REGULATES THE GENE EXPRESSIONS OF VARIOUS KEY MOLECULES IN RHEUMATOID SYNOVIAL FIBROBLASTS

Koji Fukuda¹, Yasushi Miura^{1,2}, Shinya Hayashi¹, Toshihisa Maeda¹, Ryosuke Kuroda¹. ¹Kobe University Graduate School of Medicine, Department of Orthopaedic Surgery, Kobe, Japan; ²Kobe University Graduate School of Health Sciences, Division of Orthopedic Science, Department of Rehabilitation Science, Kobe, Japan

Background: Fas ligand (FasL) is a member of tumor necrosis factor superfamily (TNFSF6) and reported to contribute to synovial hyperplasia of rheumatoid arthritis (RA). Apoptosis of RA synovial cells through Fas/FasL pathway was inhibited by pro-inflammatory cytokines present within the synovium [1]. We previously reported that decoy receptor 3 overexpressed in rheumatoid synovial fibroblasts (RA-FLS) stimulated by TNF α protects the cells from Fas-induced apoptosis [2].

Objectives: In this study, we investigated the gene expression profiles regulated by FasL in RA-FLS to reveal how FasL is involved in the pathogenesis of RA.

Methods: RA-FLS were obtained during total knee replacement surgery from patients with RA. Four individual lines of primary cultured RA-FLS were incubated either with 1000 ng/ml of recombinant human FasL protein or the same volume of phosphate buffered saline as unstimulated control in reduced serum medium for 12h. Gene expressions were detected by microarray assay (Human Genome U133 Plus 2.0, GeneChip[®] 3' Expression Array; Thermo Fisher Scientific).

Results: Microarray data analysis revealed that FasL up-regulated or down-regulated the expression of various genes in RA-FLS. The function of regulated genes included transcriptional activator activity, positive regulation of metabolic process, positive regulation of cellular metabolic process, positive regulation of macromolecule metabolic process, positive regulation of nitrogen compound metabolic process, regulation of phosphorylation, positive regulation of biological process, regulation of phosphate metabolic process, regulation of MAPK cascade, and regulation of multicellular organismal process. The most up-regulated 3 genes by FasL were dual specificity phosphatase 6 (DUSP6), epiregulin (EREG) and interleukin11 (IL-11). The most down-regulated 3 genes by FasL were angiopoietin-like 7 (ANGPTL7), protein inhibitor of activated STAT2 (PIAS2) and growth differentiation factor 5 (GDF5).

Conclusion: DUSP6 regulates CD4⁺ T-cell activation and differentiation by inhibiting the T-cell receptor-dependent extracellular signal-regulated kinases 1 and 2 activations [3]. EREG is increased in patients with RA and associated with the development of cytokine-induced arthritis [4]. IL-11 regulates the growth and development of hematopoietic stem cells and decreases the pro-inflammatory cytokines and nitric oxide productions [5]. ANGPTL7 is pro-angiogenic factor [6] and promotes pro-inflammatory responses through the P38 signaling pathway [7]. PIAS proteins inhibit the activated STAT and are involved in the pathogenesis of RA [8]. GDF5 is associated with joint destruction of patients with OA and RA [9]. FasL regulates the expression of various genes in RA-FLS. Therefore, FasL may affect the pathogenesis of RA by regulating gene expressions of these molecules in RA-FLS.

REFERENCES:

- [1] Wakisaka S. et al., Clin Exp Immunol. 1998;114:119-128.
- [2] Hayashi S. et al., Arthritis Rheum. 2007;56:1067-1074.
- [3] Bertin S. et al., Mucosal Immunol. 2015;8:505-515.
- [4] Harada M. et al., J Immunol. 2015;194:1039-1046.
- [5] Moreland L. et al., Arthritis Res. 2001;3:247-252.

[6] Katoh Y. et al., Int J Mol Med. 2006;17:1145-1149.

[7] Quian T. et al., Inflammation. 2016;39:974-985.

[8] Lao M. et al., J Immunol. 2016;196:596-606.

[9] Martinez A. et al., Ann Rheum Dis. 2008;67:1352-1353.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.2928

THU0030 THE DIFFERENTIAL EFFECT OF TNF-A AND IL-6R BLOCKERS ON THE EXPRESSION OF IL-17 AND ACTIVATED CD4⁺CD25⁺ T CELLS IN PATIENTS WITH PSORIATIC ARTHRITIS

Smadar Gertel^{1,2}, Ari Polachek^{1,2}, Victoria Furer^{1,2}, Daphna Paran^{1,2}, Ori Elkayam^{1,2}. ¹Tel Aviv Sourasky Medical Center, Department of Rheumatology, Tel Aviv-Yafo, Israel; ²Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

Background: TNF- α blockers are effective drugs for the treatment of psoriatic arthritis (PsA) and rheumatoid arthritis (RA). On the other hand, while interleukin-6 receptor (IL-6R) blockers have emerged as effective drugs in the treatment of RA, their effect in PsA has been disappointing. We hypothesized that the differential effect of TNF- α and IL-6R blockers in PsA may be mediated by the effect of these drugs on IL-17 expression, a cytokine profoundly involved in PsA and by their influence on activated CD4⁺CD25⁺ T cells.

Objectives: To evaluate the differential effect of adalimumab (ADA) (representing TNF- α blockers) and tocilizumab (TCZ) (IL-6R blocker) on the expression level of IL-17 and on the frequency of activated CD4⁺CD25⁺ T cells.

Methods: Levels of IL-17 mRNA expression were measured following *in vitro* co-culture of peripheral blood mononuclear cells (PBMC) derived from PsA patients with, ADA, TCZ at 10ug/ml or with medium alone as control for 3 days. Next, RNA was extracted and real-time PCR for IL-17 mRNA expression was performed. In addition, after 5 days incubation with the biologic agents the frequency of activated CD4⁺CD25⁺ T cells were analyzed by flow cytometry.

Results: The differential effect of ADA and TCZ on IL-17 mRNA expression and modulation of activated CD4⁺CD25⁺ T cells in culture of PBMC derived from PsA patients is shown in Figure 1. We found that IL-17 mRNA expression in PsA patients derived PBMC (n=20) was down-regulated by ADA. This down grading was significant in comparison with TCZ and medium control respectively ($p<0.0001$, $p=0.0003$). On the other hand, TCZ significantly up-regulated the expression of IL-17 as compared to medium control ($p=0.05$) (Figure 1A). The frequency of activated CD4⁺CD25⁺ T cells was down-regulated by ADA as compared to medium and TCZ, respectively ($p=0.03$, $p=0.005$), whereas activated CD4⁺CD25⁺ T cells were up-regulated by TCZ (although not significantly) as compared to medium control (n=60) (Figure 1B).

Abstract THU0030 – Figure 1. ADA and TCZ differentially modulates IL-17 mRNA expression and activated CD4⁺CD25⁺ T cells in PBMC derived from PsA patients. PBMC were co-cultured in the presence of ADA, TCZ or medium alone as a control. (A) After 72 h incubation RNA was extracted and real-time PCR for quantification of IL-17 was performed. (n=20). (B) After 5 days incubation change in %CD4⁺CD25⁺ T cells was determined by flow cytometry (n=60), ns=not significant.

Conclusion: Our data highlight the differential effect of ADA and TCZ on IL-17 expression level and on frequency of activated CD4⁺CD25⁺ T cells in culture of peripheral immune cells derived from PsA patients. This data suggest a new mechanism of action of ADA and provide a possible explanation of the inefficacy of TCZ in PsA.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.2735