weeks. After the 2nd dose she began with abdominal pain and increased depositions. Acute phase reactants were increased major PCR 194 mg/dl ESR 87 mg/dl. In colonoscopy, biopsies objective and inflammatory lesions with extensive areas of mucosal ulceration compatible with Crohn's disease were observed.

Case 2 A 59-year-old man with a diagnosis of ankylosing spondylitis of 30 years of evolution without a clinical response to NSAIDs and sulphasalazine, was treated with SEK 150 mg. After the second dose during induction, He presented fever 38.9°C, abdominal pain, bloody diarrhea, and nocturnal tenesmo. A colonoscopy showed typical ulcerative colitis lesions with severe activity.

Conclusions SEK is a very potent treatment for psoriasis and psoriatic arthritis, with positive results in Spondylitis, but not effective for IBD. IL-17 is a cytokine with a role in the normal intestinal homeostasis.

Psoriasis and Spondyloarthritis patients have an association with IBD and uveitis.

We present 2 patients who were diagnosed of IBD shortly after start SEK, anti-IL17. We think they could have a previous undiagnosed IBD; SEK could have trigger a flare but We can't rule out a role of IL-17 inhibition. During clinical trials for SEK, only 0.7 cases per 100 patients-year of IBD were reported. Caution must be taken before start SEK for patients to detect possible symptoms of IBD.

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Disclosure of Interest None declared.

P096

THE ROLE OF THE IL-23/TH17 AXIS AS MODULATOR OF B CELL-MEDIATED (AUTO)IMMUNE RESPONSES

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Career situation of first and presenting author Post-doctoral fellow.

Introduction Rheumatoid arthritis (RA) is characterized by chronic synovitis and joint destruction. Autoantibodies and autoreactive B cells are a hallmark of RA. Furthermore, Th17 cells have been demonstrated to be crucial for disease development. However, checkpoints and mechanisms regulating the onset of rheumatoid arthritis (RA) remain largely unclear.

Objectives Recently, we have demonstrated, that Th17 cells suppress the enzyme ST6 a-galactoside b-2,6-sialyltransferase in developing plasma cells. Thereby, Th17 cells are able to increase the inflammatory activity of autoantibodies in an IL-23 dependent manner by regulating the degree of Fc-glycosylation. However, the molecular mechanisms that mediate this IL-23/Th17-mediated proinflammatory reprogramming of B cells and the relevance for arthritis remains to be determined in detail.

Methods K/BxN mice were treated twice a week with neutralizing antibodies against IL-17A and IL-22 from week 1 until week 9. Both, clinical, histological and immunological parameters of arthritis were assessed. Serum was collected weekly and autoantibody titers were determined using ELISA. Collected Sera were used for K/BxN serum transfer to evaluated IgG activity. Additionally, the expression levels of the corresponding interleukin receptors (IL17RA and IL22Ra1) were analyzed during collagen-induced arthritis.

Results Here we show, that in contrast the upregulation of IL-22Ra1 on plasmablasts in the spleen, lymph node and bone-marrow during collagen-induced arthritis, its blockade during K/BxN arthritis did not prevent the onset of arthritis. Also, the IgG from K/BxN mice remained its inflammatory activity. We also show, that while IL17RA is basically absent on B cells during arthritis, the neutralization of IL-17A during K/BxN arthritis led to a strongly delayed development of autoimmune arthritis. Furthermore, depletion of IL17A led to a decreased titer of autoantibodies during early phases of K/BxN arthritis. However, in the K/BxN serum transfer mice which received serum that was produced in the absence of IL-17 were not protected against inflammatory arthritis.

Conclusions Our data indicate that IL-22 is not directly involved in the regulation of IgG activity during K/BxN arthritis. Furthermore, our data indicate that IL-17A is indeed a crucial cytokine during inflammatory processes inside the joint and may be involved in the germinal center reaction or plasma cell survival. However, neither IL-17 nor IL-22 is involved in the IL-23/Th17-mediated proinflammatory reprogramming of B cells to produce highly pathogenic autoantibodies. Therefore, other cytokines produced by Th17 cells and/or mechanisms depending on cell-cell contact proteins might orchestrate the Th17/B-cell crosstalk leading to the downregulation of St6gal1 in developing plasma cells.

Disclosure of Interest None declared.

P097

INTRACELLULAR INTERLEUKIN-1 RECEPTOR ANTAGONIST RELEASED UPON CELL DEATH ACTS AS AN ALARMIN INHIBITOR IN ALDARA CREAM-INDUCED PSORIASIS-LIKE SKIN INFLAMMATION

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Introduction The inflammatory effects of interleukin (IL)-1 are tightly controlled by IL-1 receptor antagonist (IL-1Ra), which blocks the binding of both IL-1 α and IL-1 β to IL-1R1. Four IL-1Ra isoforms are produced from the same gene by the use of different first exons, alternative mRNA splicing and translation initiation sites. One IL-1Ra isoform is secreted (sIL-1Ra), whereas the three others are intracellular (icIL-1Ra1, 2, 3) due to the absence of a signal peptide. In contrast to the well-characterized function of the secreted isoform, the biological role of the intracellular isoforms remains largely unclear. The icIL-1Ra1 isoform is constitutively expressed and represents the major isoform in keratinocytes.

Objectives To investigate the role of icIL-1Ra1 in a mouse model of psoriasis-like skin inflammation induced by Aldara cream, an FDA-approved drug with the active ingredient imiquimod, a toll-like receptor 7 agonist.

Methods We generated a mouse line specifically lacking icIL-1Ra1, in which expression of the other three IL-1Ra isoforms was not affected. Psoriasis-like skin inflammation was induced on mouse ears by the topical application of Aldara cream. Skin inflammation was assessed using a caliper to measure ear thickness. Ear mRNA levels of cytokines were measured by real-time PCR. An intracellular or extracellular role of icIL-1Ra1 was investigated *ex vivo* on ear biopsies and *in vitro* in primary keratinocytes by real-time PCR or ELISA.

Results Naïve icIL-1Ra1 deficient mice exhibited a normal phenotype. However icIL-1Ra1 deficiency resulted in an enhanced severity of Aldara cream-induced skin inflammation as demonstrated by increased ear thickness. In addition, mRNA levels of several pro-inflammatory cytokines were significantly increased in icIL-1Ra1 deficient mice as compared to wild-type (WT) littermates. By immunofluorescence IL-1Ra was detected only in keratinocytes of naïve and Aldara-treated WT mice, but totally absent in icIL-1Ra1 deficient mice. Using ear biopsies and keratinocytes from WT mice, we observed that Aldara cream led to the release of both icIL-1Ra1 and the alarmin IL-1 α , accompanied by caspase 1/11-independent cell lysis. Injection of neutralizing anti-IL-1 α antibodies into Aldara-treated icIL-1Ra1 deficient mice significantly reduced the severity of skin inflammation.

Conclusions These data suggest that icIL-1Ra1 is stocked in keratinocytes in order to immediately counteract the inflammatory effects of IL-1 α that is released upon cell lysis, thus acting as an intrinsic alarmin inhibitor.

Disclosure of Interest None declared.

P099

COMPARISON OF IL-17A AND IL-17F EFFECTS ON DIFFERENT CELL TYPES

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Career situation of first and presenting author Post-doctoral fellow.

Introduction IL-17A has effects on a growing number of cell types, including synoviocytes, skin fibroblasts or endothelial cells. IL-17A is now a therapeutic target in several inflammatory diseases, including psoriasis, PsA and SPA. IL-17F is the closest member of IL-17A in the IL-17 family and it shares IL-17A biological activities. It is now of interest to target both IL-17A and F. Furthermore, IL-17A and IL-17F can synergize with other cytokines such as TNF or IL-1.

Objectives The aim of this study is to compare in the same experiments, the effect of IL-17A and IL-17F, in combination or not with TNF and IL-1 β , on pro-inflammatory cytokine production (IL-6 and IL-8) first by RA synoviocytes, then extended to other cell types.

Methods Cells (RA synoviocytes, psoriatic skin fibroblasts, human umbilical vein endothelial cells, myoblasts and hepatocytes) were cultured in presence or not of: IL-17A alone, IL-17F alone, TNF alone, IL-1 β alone or combinations, IL-17A/TNF, IL-17A/IL-1 β , IL-17A/TNF/IL-1 β , IL-17F/TNF, IL-17F/IL-

1 β IL-17F/TNF/IL-1 β . After 48 hour of culture, supernatants were recovered and IL-6 and IL-8 levels were measured by ELISA. A data analysis of microarrays, done on synoviocytes, was realized.

Results IL-17A and IL-17F alone increased significantly both IL-6 and IL-8 production by synoviocytes, with a higher efficiency for IL-17A. For IL-6, TNF and IL-1 β alone had the largest effect on myoblasts, increasing 5 fold the secretion, while for IL-8 it was on skin fibroblasts, increasing at least 5 fold the production. The synergy between IL-17A and TNF was observed on all cells for IL-6 secretion, and for IL-8, only endothelial cells did not show a synergistic effect. For IL-17F and TNF, except endothelial cells, a synergy was also observed, however less powerful than IL-17A/TNF. The effect of the combination IL-17A/IL-1 β or IL-17F/IL-1 β was more dependent on the cell type, with an additive effect for synoviocytes, and a synergistic effect for hepatocytes. The effect of combination of the three cytokines could induce an additive effect as for synoviocytes or a synergistic effect as for skin fibroblasts. The analysis of microarrays showed 1346 regulated probes, with a measured modulation of more than 2 fold, and 279 probes more than 4 fold, with a stronger effect of IL-17A/TNF combination on cell signalization compared to IL-17F/TNF or each cytokine alone.

Conclusions IL-17A and IL-17F act in a similar way on the different cell types, by inducing pro-inflammatory cytokine secretion. The difference was the intensity of the response, where IL-17A induced a higher effect than IL-17F. IL-17A and IL-17F activities were potentiated by the combination with TNF and IL-1 β . The effect of these combinations on cytokine production was dependent on cell types. These differences may explain different response to treatment according to the primary cell type involved in disease.

Disclosure of Interest None declared.

P100

SYSTEMIC AND LOCAL IL-17A AND MIR-146A LEVELS IN RHEUMATOID ARTHRITIS PATIENTS

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Introduction Interleukin 17 (IL-17) is a proinflammatory cytokine, which has been recognized as an important cytokine in the pathogenesis of rheumatoid arthritis (RA).¹ Altered systemic and local expression of specific microRNAs (miRNAs) was been reported in samples of RA patients.² It has been found that miR-146a was associated with IL-17 expression in IL-17 producing T-cells in the synovium thus indicating its possible role in RA pathogenesis via IL-17 expression.³

Objectives To examine a possible deregulation of the expression levels of miR-146a and levels of IL-17A in peripheral blood (PB) and synovial fluid (SF) of RA patients.

Methods Expression levels of miR-146a were determined in matched PB and SF samples of RA patients by relative quantitation method 2^{- $\Delta\Delta C_t$} . As reference control for normalization RNU6B gene was used. Receiver operating characteristic (ROC) curve analysis using RQ values was constructed in