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.

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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