to healthy skin[1]. ACKR2 is a scavenging receptor of inflammatory CC chemokines and has been proposed as a regulator of cutaneous inflammation in psoriasis. It has not been studied in PsA.

Objectives: To compare the transcriptome of PsA lesional, PsA uninvolved and healthy control skin and evaluate ACKR2 expression in PsA.

Methods: Biopsies were taken from healthy control (HC) skin and paired lesional and uninvolved skin from patients with PsA. Libraries for bulk RNA sequencing were prepared from polyA selected RNA and sequenced on NovaSeq 6000. Sequencing data were analysed using Seurat2. ACKR2 mRNA expression was validated by qPCR. RNAscope was used to localise ACKR2 expressing cells and sections were co-stained with podoplanin or stained in serial sections with CD45. Chemokine protein expression in skin was evaluated using Luminex technology.

Results: Nine HC and 9 paired skin samples from patients with PsA were sequenced. The PsA skin lesions (PsA L) formed a distinct population in the transcriptomic principal component analysis (PCA) plot while HC and PsA uninvolved skin (PsA U) were overlapping. Only 15 genes were differentially expressed between HC and PsA L and none coded for chemokines. There were however significantly upregulated chemokines and receptors in PsA L. Unexpectedly, ACKR2 was the 2nd most upregulated chemokine receptor in PsA L with unchanged expression in PsA U compared with HC (PsA L vs HC log2fold 3.38, p.adj=9.51E-41; PsA L vs PsA U log2fold 3.58, p.adj=3.2E-45; PsA U vs HC log2fold -0.2, p.adj=0.732).

The upregulation of ACKR2 in PsA L and unchanged expression in PsA U was confirmed by qPCR. RNAscope demonstrated strong expression of ACKR2 in the suprabasal layer of the epidermis in PsA L. In HC and PsA U, only occasional ACKR2 positive cells were seen in the epidermis. ACKR2 was expressed in lymphatic vessel walls but was not observed in CD45+ leukocytes. Provisional skin chemokine protein expression data showed poor correlation between mRNA levels and protein expression for the ACKR2 ligands CCL2, CCL3, CCL7, CCL8, CCL11, CCL13 and CCL22 in HC and PsA U, with negative correlation between ACKR2 mRNA expression and CCL2, CCL8 and CCL11 protein expression. In PsA L, chemokine mRNA correlated with protein expression, but protein expression of chemokine ligands did not correlate with ACKR2 expression.

Conclusion: This data set shows expected upregulation of chemokines and their receptors in PsA L but relatively unchanged gene expression in PsA U, which contrasts to previous studies in psoriasis. This study demonstrates a strong upregulation of ACKR2 in keratinocytes in PsA L, with unchanged expression in PsA U. The RNA expression and protein expression data suggest that ACKR2 has little effect on the levels of its ligands in PsA skin lesions. However, this study may have missed local effects of ACKR2 in the epidermis.

References:

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