Immunoglobulins are upregulated in psoriatic arthritis skin lesions but not in psoriasis skin lesions.

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Background and Aims

- Up to 30% of patients with psoriasis develop psoriatic arthritis (PsA).
- The traditional assumption is that the skin disease is the same in both, although a previous proteomic analysis found differences [1], and a comparison of skin RNA sequencing presented at the GRAPPA Trainee symposium in 2020 suggested transcriptomic differences in skin homeostatic and immune pathways in skin lesions.
- This project further evaluated differences in immunoglobulin gene expression in skin lesions in psoriasis and PsA.

Methods

- Full thickness skin biopsies were obtained from healthy controls (HC) and paired PsA lesional and uninvolved skin.
- Whole tissue PolyA selected RNA was sequenced on NovaSeq 6000.
- Psoriasis comparator: patients with psoriasis without PsA obtained by Tsoi et al 2019 [2] (GEO accession GSE121212).
- PsA validation cohort: Patients with PsA from the GSE121212 dataset.
- Data analysis: Searchlight2 [3].

Results

	PsA (n=9)	HC (n=9)	Tsoi PsO (n=16)	Tsoi HC (n=16)
Age (years) mean (95% CI)	46.44 (33.94; 58.95)	36.44 (29.57; 43.32)	37.44 (30.17; 44.71)	37.13 (30.32; 43.93)
Female gender (%)	5 (55.6%)	6 (66.7%)	6 (37.5%)	6 (37.5%)
PASI median (25th; 75th)*	5.3 (5.2; 10.8)		5.0 (3.5; 6.8)	

Table 1. Participant characteristic *data missing for 2 participants with psoriasis body surface area 3%.

There are >6000 significant DEGs in psoriasis and PsA lesions compared with HC.

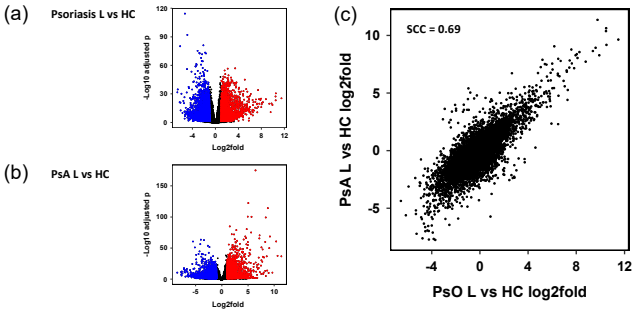

Figure 1. DEGs in skin lesions vs HC skin. Volcano plots for the comparisons psoriasis lesions vs HC (a) and PsA lesions (PsA L) vs HC (b). A positive fold change indicates higher expression in skin lesions than in HC. (c) Relationship between the log2 fold changes for psoriasis lesions (PsO L) vs HC and PsA L vs HC. Each dot represents one gene. SCC = Spearman Correlation Coefficient (SCC).

Pathway enrichment of adaptive immune response and B cell mediated immunity genes in PsA skin lesions.

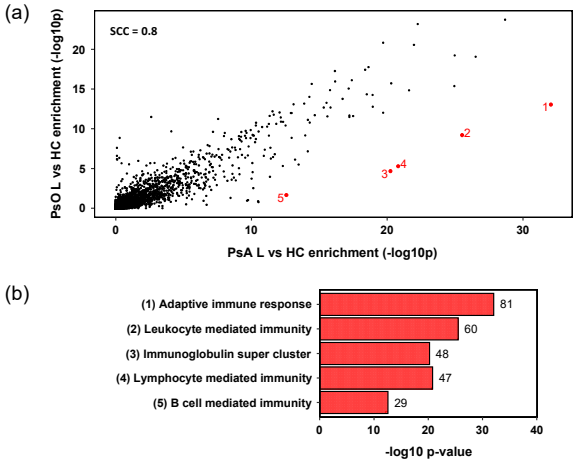

Figure 2. Pathway enrichement in psoriasis and PsA skin lesions. (a) Relationship between gene ontology enrichment for psoriasis lesions (PsO L) vs HC and PsA lesions (PsA L) vs HC. Each dot represents one gene ontology. The 5 ontologies with the largest absolute difference in enrichment are in red, and shown in the bar charts in (b). The -log10 enrichment p-value is given on the x-axis and the ontology name on the y-axis. Data labels represent the number of significantly differential expressed genes within each gene set.

PsA skin lesions are enriched in immunoglobulin genes

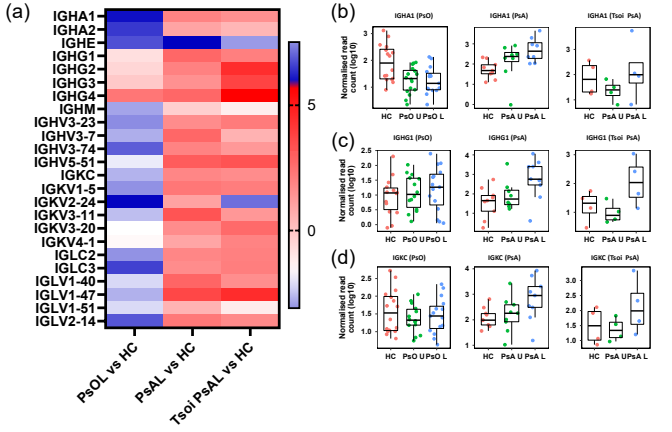

Figure 3. Change in immunoglobulin gene expression in psoriasis and PsA skin lesions. (a) Heatmap of the log2 fold change in immunoglobulin gene expression (y-axis) in skin lesions compared to HC skin for the comparisons given on the x-axis. Log10-transformed, normalised read counts in individual samples were plotted for the immunoglobulin genes IGHA (b), IGHG1 (c) and IGKC (d).

Conclusion

- Psoriasis and PsA skin lesions share many transcriptional changes and pathway enrichments.
- Immunoglobulin genes are upregulated in PsA specifically.
- Future studies are required to determine if a differential immune response within the skin lesions with generation of autoantibodies facilitates the spread of inflammation from the skin to joints in PsA.

Enrichment of transcription factor POU2F1 in PsA lesions

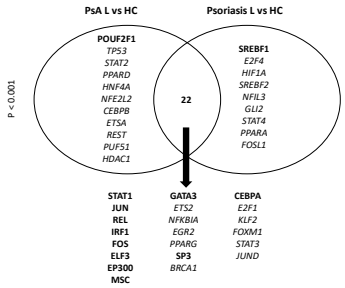

Figure 4. Enriched upstream regulators in psoriasis and PsA skin lesions identified by TRRUST analysis. Commonly enriched transcription factors are shown below the diagram. The ten most significantly enriched upstream regulators in each comparison are in bold font. The p-value for the overlap (hypergeometric test) is given.

References
1. Cretu, D., et al., *Quantitative tandem mass-spectrometry of skin tissue reveals putative psoriatic arthritis biomarkers.* Clin Proteomics, 2015. **12**(1): p. 1. **2.**Tsoi, L.C., et al., *Atopic Dermatitis Is an IL-13-Dominant Disease with Greater Molecular Heterogeneity Compared to Psoriasis.* J Invest Dermatol, 2019. **139**(7): p. 1480-1489. **3.** Cole, J.J., et al. *Searchlight: automated bulk RNA-seq exploration and visualisation using dynamically generated R scripts.* BMC Bioinformatics 22, 411 (2021). https://doi.org/10.1186/s12859-021-04321-2