Serum proteomic analysis of cellular immune clusters in psoriatic arthritis

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INTRODUCTION

Our recent study used unsupervised cluster analysis of peripheral blood mass cytometry data to characterize immune cell profiles in patients with psoriatic arthritis (PsA) (Figure 1).

We identified a cluster (Cluster 1) enriched with CD4+ memory T cells, which was associated with poorer response to biologic therapy and more severe PsA phenotype[1].

Further characterization of these immune profiles may enhance our understanding of PsA phenotypes

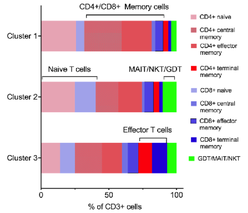


Figure 1: Distribution of CD4+ and CD8+ subsets by cluster

OBJECTIVE

We aim to characterize the proteomic profile of the CD4+ memory T cell profile in comparison with the other two immune profiles and identify key proteins and biological pathways associated with disease severity and treatment outcomes.

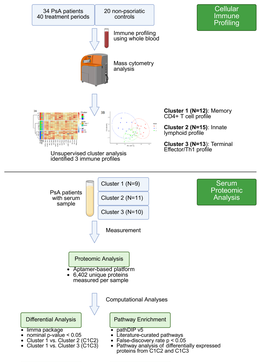
METHODS

Setting and Population
Patients with active PsA were recruited from a single academic center in Toronto, Canada

Cellular Immune Profiling and Clustering
34 peripheral blood samples collected to assess circulating immune cell populations using mass cytometry (40 treatment periods). Unsupervised cluster analysis identified three cluster profiles based on cellular profiles

Serum Proteomic Analysis
30 patients had serum available for proteomic analysis on an aptamer-based platform. 6,402 unique proteins were measured per patient

Bioinformatic Analysis
Differential expression analysis was performed comparing proteomic expression between Cluster 1 and Cluster 2 (C1C2) and Cluster 1 and Cluster 3 (C1C3) ($p < 0.05$). Differentially expressed proteins were inputted into pathDIP v5 for pathway enrichment analysis, Networks were created using NAViGaTOR v3



RESULTS

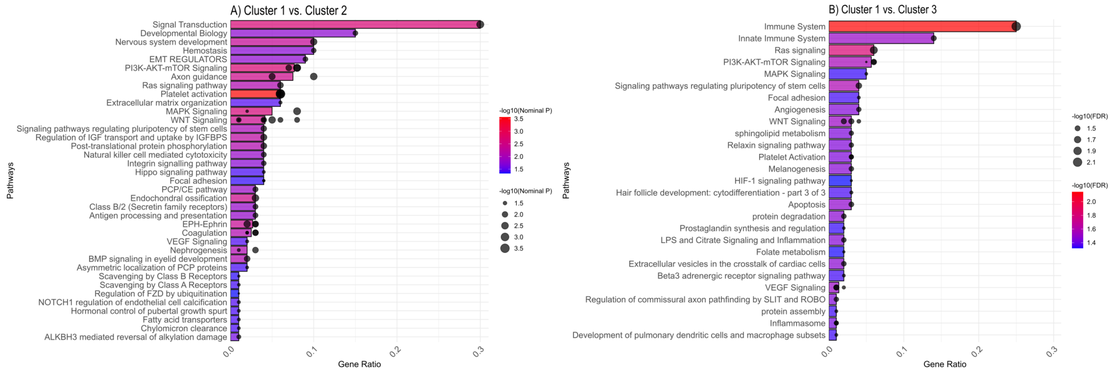


Figure 2: Pathway enrichment of differentially expressed proteins (DEPs) across cluster 1 and cluster 2 (A) and cluster 1 and cluster 3 (B). Bar plot showing pathways (Y-axis) ranked in descending order based on gene ratio (X-axis). Dots represent the number of related pathways and the size indicates the significance

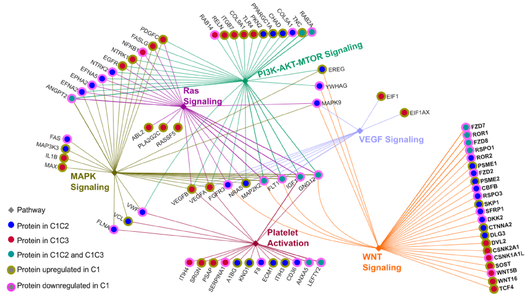


Figure 3: Protein-pathway network of the shared pathways between C1C2 and C2C3. Shared pathways are represented as coloured diamond nodes and proteins as circular nodes. Blue circular node denotes a protein differentially expressed in C1C2, red for proteins in C1C3 and teal for proteins in both comparisons. An olive diamond highlight denotes a upregulated protein in C1, whereas a pink diamond highlight is for downregulated protein in C1

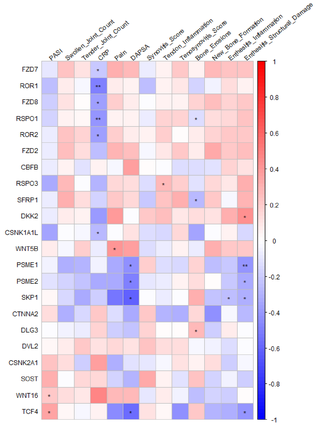


Figure 4: Correlation matrix of the relationship between DEPs belonging to the WNT signaling pathway and PsA disease features. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

RESULTS

287 DEPs identified between C1C2 and 351 DEPs between C1C3

The untargeted proteomic approach revealed a predominant enrichment of pathways related to intracellular signaling cascade (e.g., Ras signaling, PI3K-AKT-mTOR signaling, MAPK signaling, WNT signaling) and downstream effectors (e.g., vascularization, platelet activation, epithelial-mesenchymal transition regulation)(Figure 2)

WNT signaling pathway was most distinct to the CD4+ memory cell profile (Cluster 1), containing highest number of DEPs unique to the pathway (Figure 3)

DEPs in WNT signaling (DKK2, WNT5b, ROR2, FZD7, FZD8, FZD2) were proteins upregulated in Cluster 1 and positively correlated with disease activity measures (Figure 4). The proteins were linked with higher DAPSA scores and higher sonographic enthesitis

CONCLUSIONS & FUTURE DIRECTIONS

We profiled the serum proteome across three PsA profiles defined by immune cell profiles to uncover key drivers of inflammation and damage

WNT signaling emerged as a notable pathway in severe PsA phenotype (memory T cell profile), with protein markers DKK2, WNT5b, ROR2, FZD7, FZD8, and FZD2 as potential biomarkers associated with sonographic enthesitis.

Our integrated mass cytometry and serum proteomic analysis suggest that deregulated WNT signaling is linked to more severe PsA phenotype and poorer therapeutic response, underscoring its potential as a diagnostic marker and a therapeutic target

Continued exploration of the biological mechanisms of PsA profiles using integrated multi-omics will deepen our understanding of disease mechanisms and advance precision medicine approaches

REFERENCES

1 Eder L, Li X, Thib S, Ganatra D, Diao L, Chandran V. Deep Cellular Immune Profiling in Psoriatic Arthritis Correlates with Imaging Phenotypes and Response to Targeted Advanced Therapy [abstract].*Arthritis Rheumatol.* 2023; 75 (suppl 9). https://acrabstracts.org/abstract/deep-cellular-immune-profiling-in-psoriatic-arthritis-correlates-with-imaging-phenotypes-and-response-to-targeted-advanced-therapy/. Accessed April 7, 2025.

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