Peripheral T-Cell Metabolic Reprogramming as a Potential Indicator of Therapy Response in Rheumatoid Arthritis

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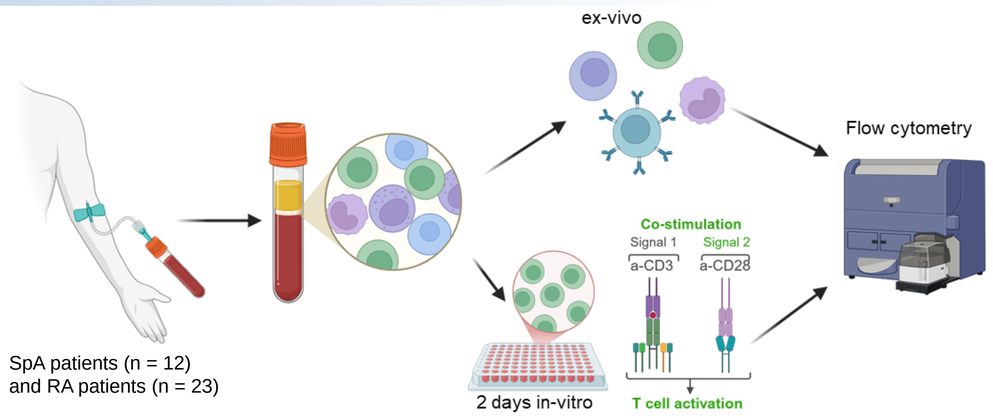
Background

Rheumatoid arthritis is an immune-mediated disease with variable therapeutic responses. T-cell metabolic reprogramming —including altered glycolysis, amino-acid (AA) or lipid metabolism (LIP), and energy stress/sensing pathways (ES), as well as dysregulated signaling pathways — contributes to chronic inflammation.

Methods



Selective shifts in anaerobic glycolysis and energy stress

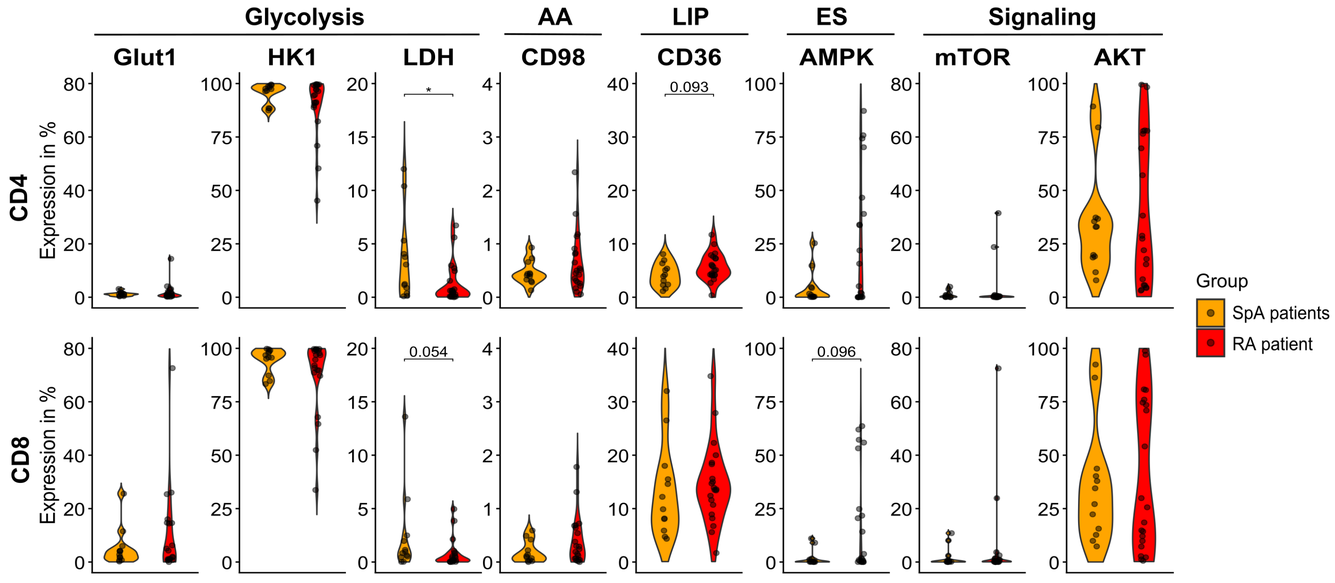


Fig.1 Global comparison of metabolic expression ex vivo. RA T-cells show reduced anaerobic glycolytic activity (LDH) and trends toward increased lipid uptake (CD36) and energy stress (AMPK), while signaling pathways remain largely comparable.

Subset-specific metabolic reprogramming of glycolysis, lipid and energy pathways

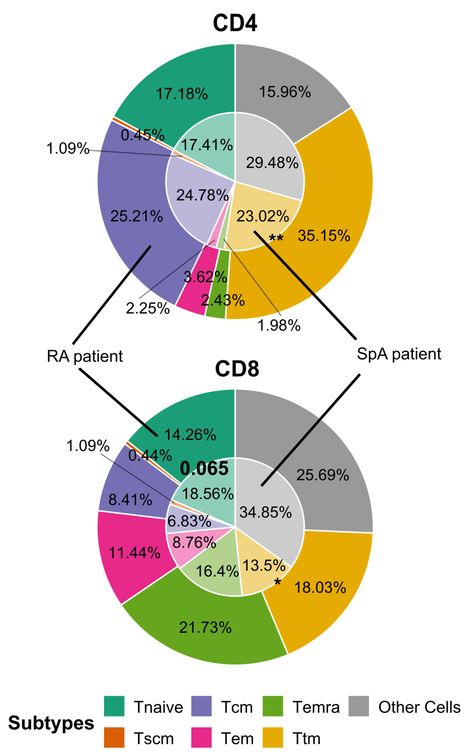


Fig.2 Frequencies of T cell subsets. RA shows increased T_{TM} in both CD4 and CD8 T cells compared to SpA, with a trend toward fewer CD8 T_{NAIVE}.

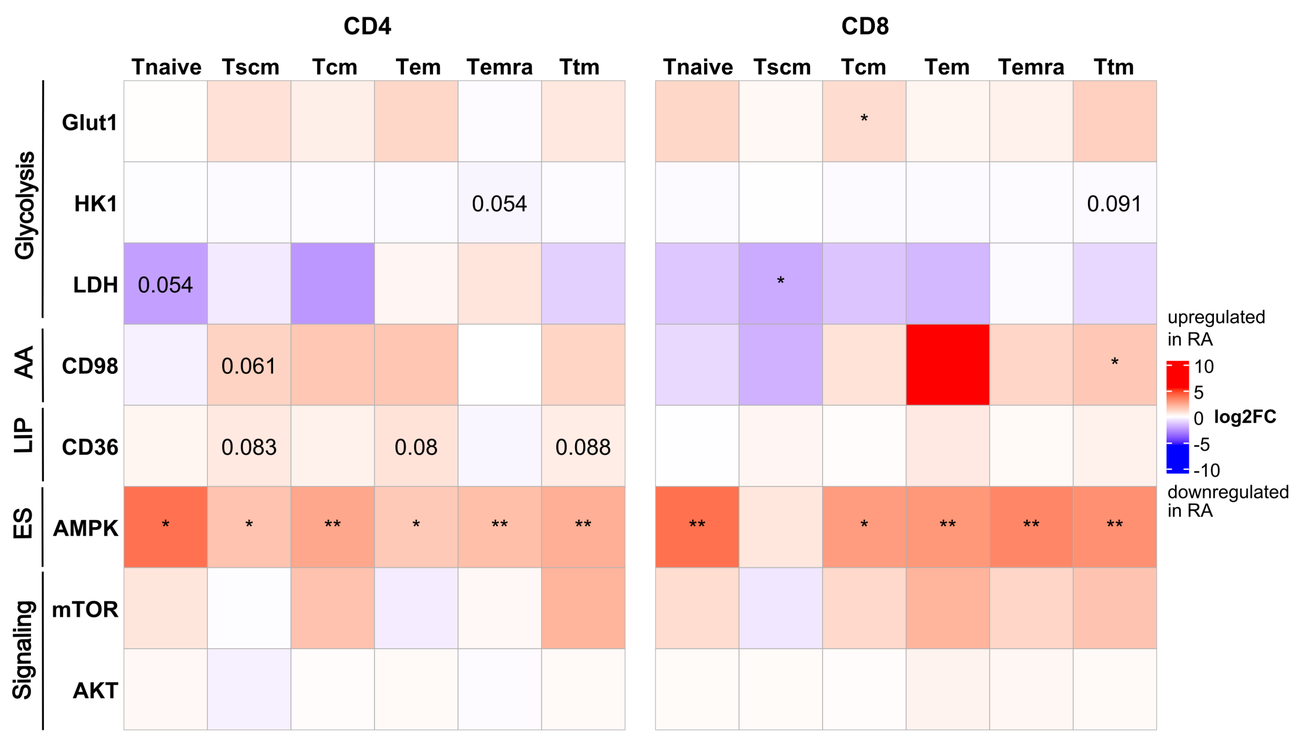


Fig.3 Metabolic expression of T-cell subsets. AMPK is broadly increased in all subsets, mTOR is generally higher but not significant, while AKT and HK1 remain largely unchanged. Glut1 is slightly elevated, CD98 and CD36 show subset-specific increases or trends, highlighting differential metabolic regulation across T-cell populations.

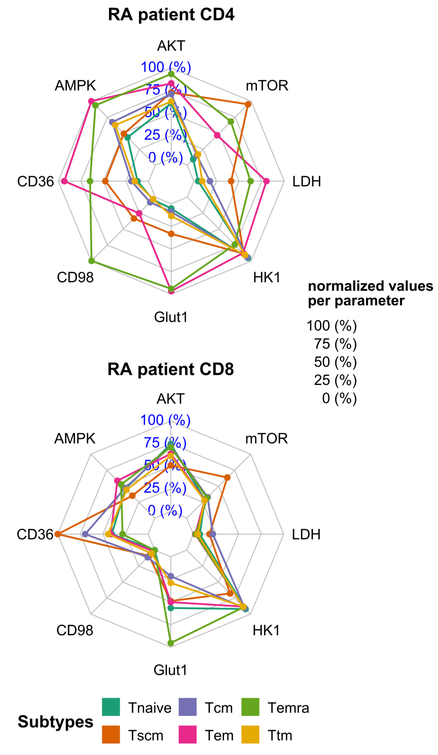


Fig.4 Metabolic patterns of subsets in RA. T_{NAIVE}, T_{CM} and T_{TM} show consistently low marker expression, T_{SCM} highest in mTOR, while CD4 exhibiting greater heterogeneity.

Stimulation-induced metabolic and signaling changes

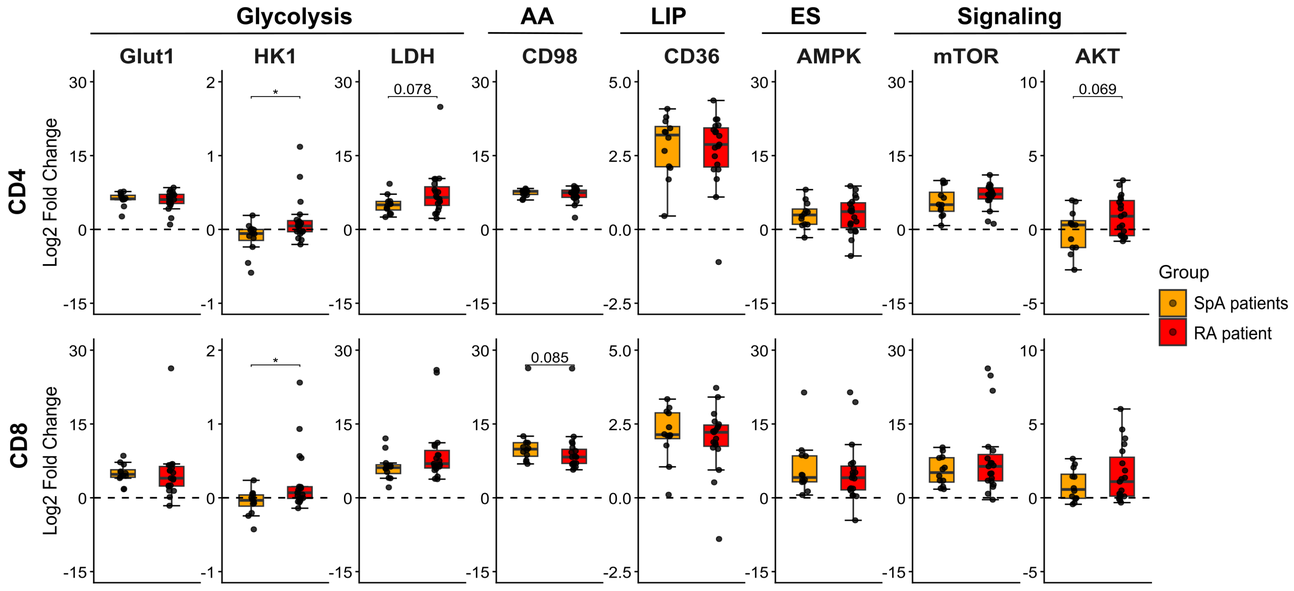


Fig.5 Change of metabolic expression from ex vivo to stimulated. HK1 shows a significantly higher increase in RA, LDH and AKT display trends toward higher induction, while CD98 shows a trend toward lower induction in RA compared to SpA.

Conclusion

- LDH, HK1, and AMPK (with CD36, CD98, and AKT) are candidate biomarkers for disease stratification.
- T_{EM}/T_{EMRA} are metabolically active, likely driving persistent inflammation in RA.
- Elevated mTOR in T_{SCM} suggests a reservoir for long-term immune activation and potential therapy resistance.
- Activation-induced metabolic changes in RA T cells follow a pattern distinct from SpA.

Future directions: Longitudinal RA analysis will assess how metabolic markers change over time and under different therapies, comparing sequential visits and responses to treatment.

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The authors declare that they have no conflict of interest

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