Tocilizumab partially reverses the altered transcriptional regulation of glycolysis in circulating CD8^{+} T cells of Rheumatoid arthritis patients

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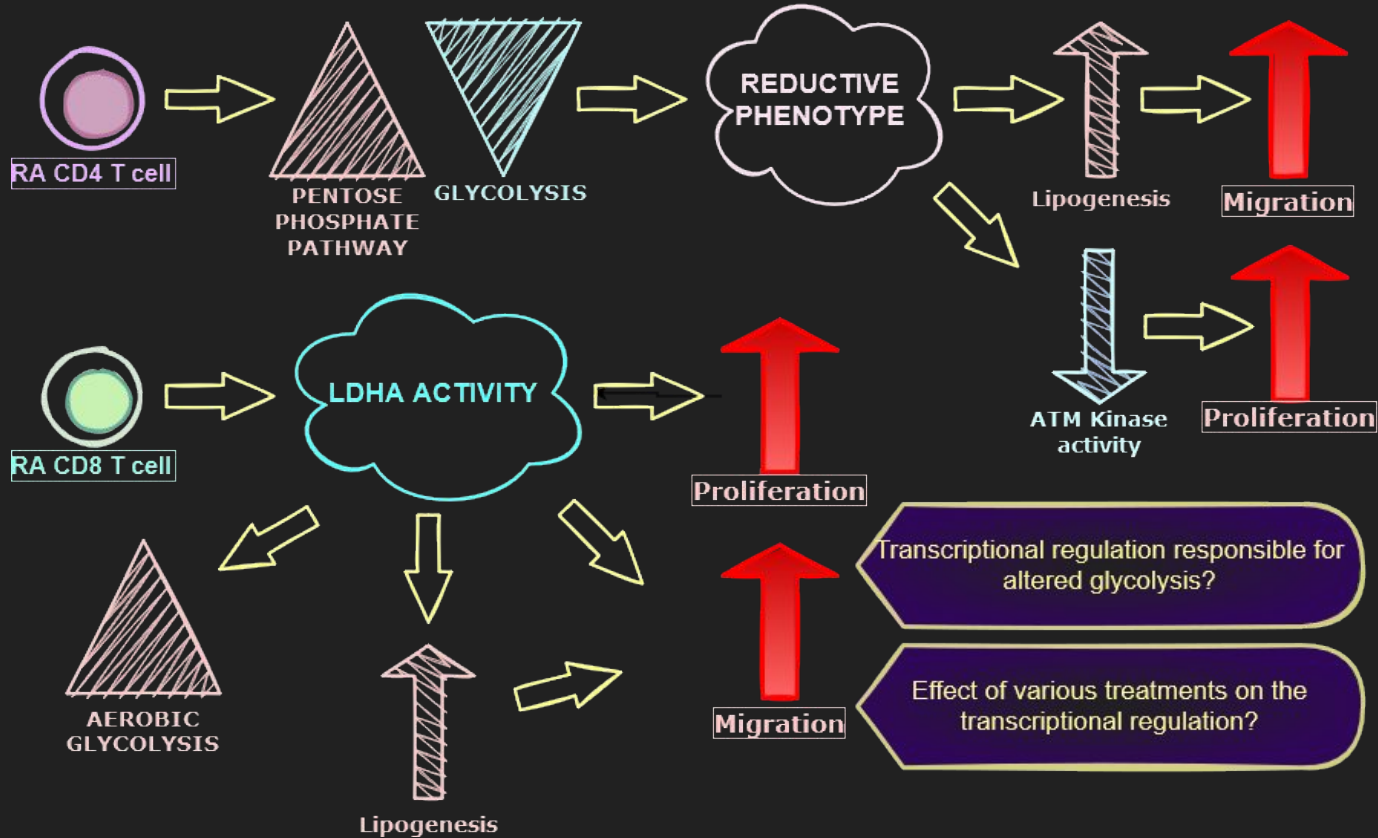[2] Manipal Academy of Higher Education, Manipal, Karnataka, India
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Background

Peripheral T cells of rheumatoid arthritis (RA) patients show pathological changes to metabolic pathways including glycolysis.

Objectives

What is the effect of treatment on the transcriptional regulation of glycolysis genes?

Methods

Publicly available RNA sequencing data from peripheral blood CD4$^+$ and CD8$^+$ T cell subsets of healthy, untreated and treated RA individuals was analysed.

The treatments included Methotrexate (MTX), Infliximab (IFX) and Tocilizumab (TCZ) therapy

Differential co-expression between transcription factors and glycolysis related genes was analysed using lioness and limma. Significantly co-expressed edges were annotated with GTRD Transcription factor-target information.
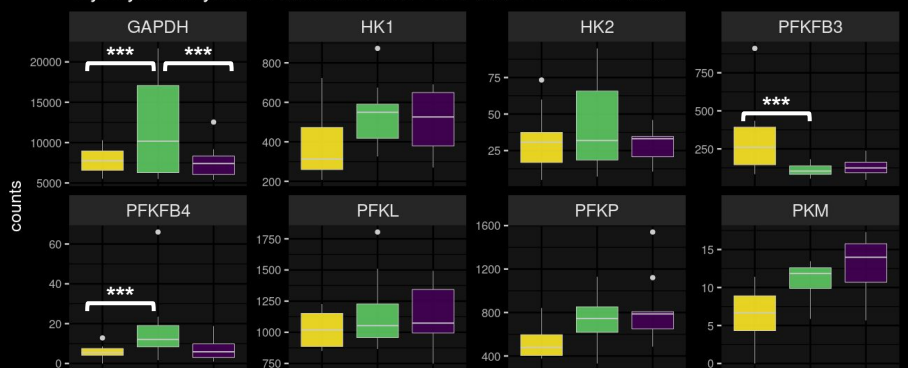
Subnetworks of high centrality genes were created.
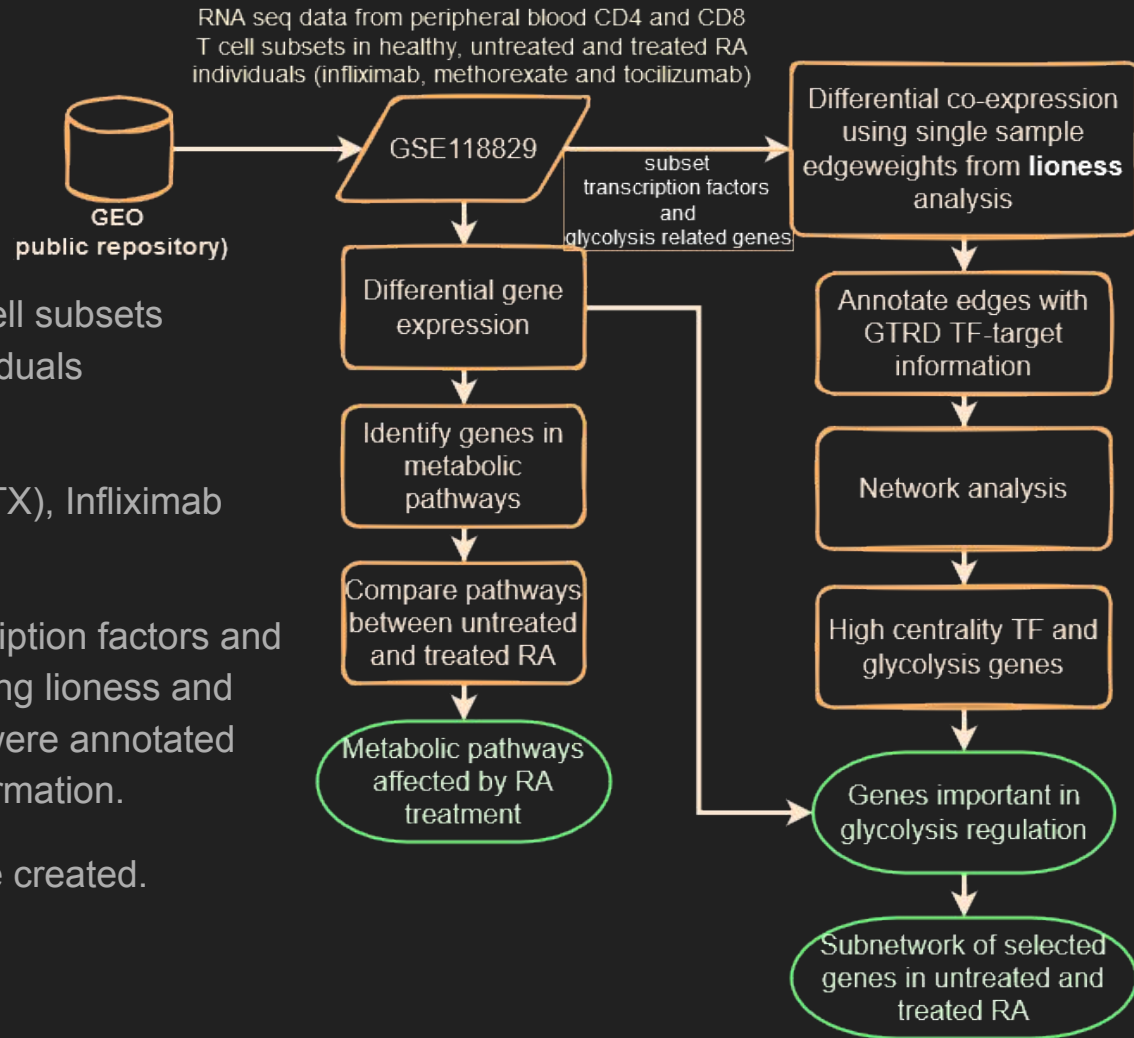
RESULTS

Expression levels of some genes in glycolysis, TCA cycle and oxidative phosphorylation in CD8$^+$ Tem cells are partially reversed by TCZ treatment.
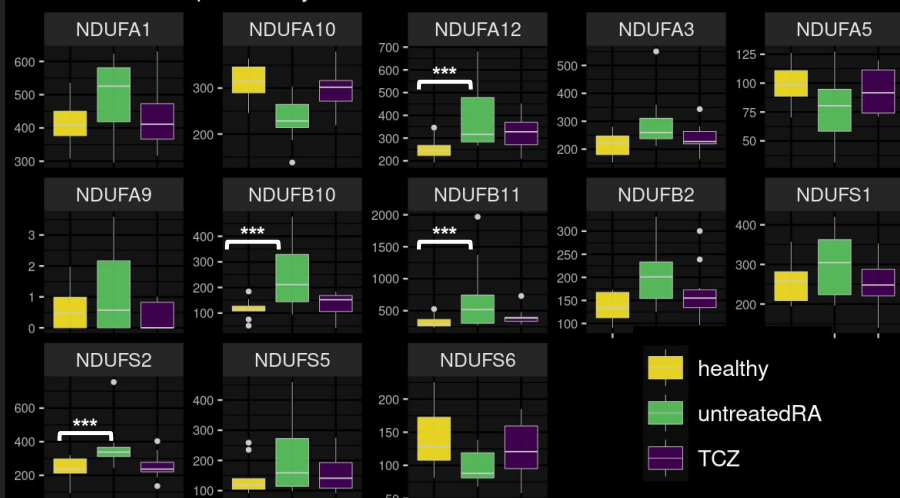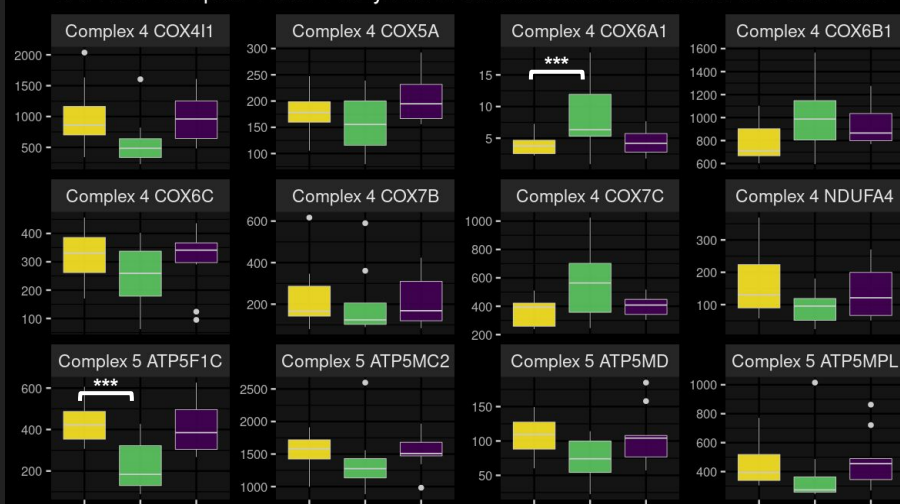
A) Expression values of GAPDH and its differentially expressed neighbors in the healthy, untreated RA and tocilizumab treated RA CD8⁺ Tem cells. Statistically significant differential expression is indicated by asterisks (***).

B) GAPDH and its neighbors in the untreated RA network. Red nodes are upregulated and blue nodes are down regulated. Purple edges show higher mean edge weight in untreated RA samples. Green edges show higher mean edge weight in healthy samples.

C) GAPDH and its neighbors in the tocilizumab treated network. Purple edges show higher mean edge weight in TCZ treated samples. Green edges show higher mean edge weight in untreated RA samples.
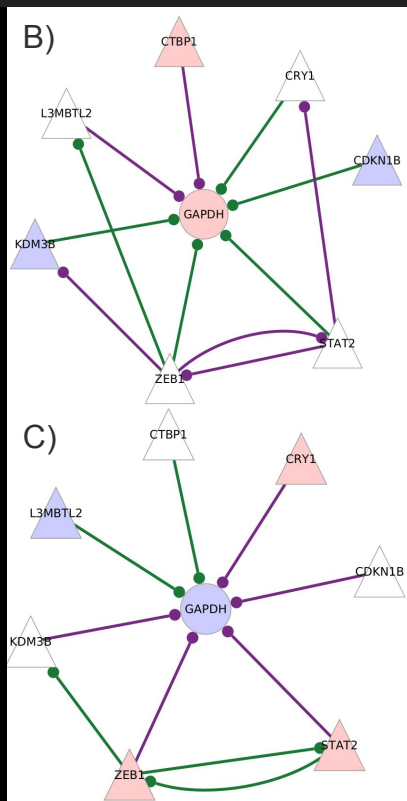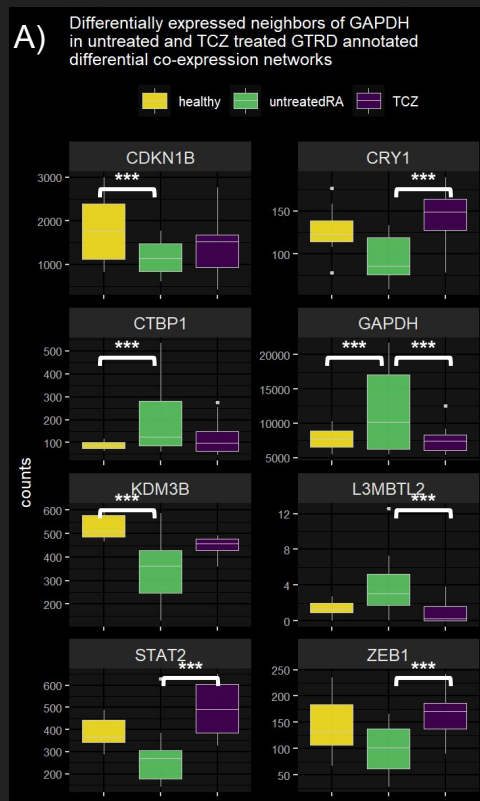
Gene expression levels and co-expression levels with GAPDH of these transcription factors were reversed in the CD8⁺ Tem cells of TCZ treated individuals

STAT1 — Interferon Signalling

KDM3B, CDKN1B — Cell Proliferation

CRY1, L3MBTL2 — DNA damage response

CTBP1 — REDOX homeostasis

CRY1 — Circadian rhythm

ZEB1 — T cell differentiation
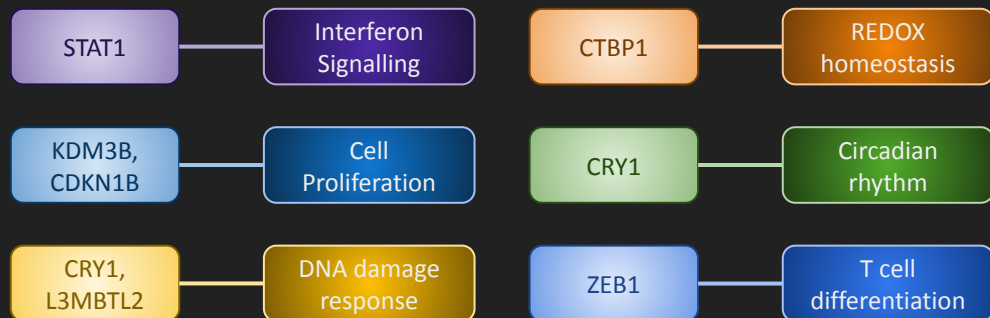
These transcription factors are associated with various non-glycolytic cellular functions.

Conclusion

Tocilizumab treatment is associated with a return to a healthy like expression state for several genes. Tocilizumab does not restore PFKFB3 levels indicating that its effect on glycolytic activity in these cells is limited. The effect of tocilizumab treatment on the expression of GAPDH involves several transcription factors which take part in various non-glycolytic functions such as T cell differentiation, proliferation, interferon signalling, REDOX homeostasis, circadian rhythm and DNA damage repair. GAPDH gene expression changes associated with TCZ treatment in CD8^{+} Tem cells of RA patients may affect these functions.

References

1. **Dataset: GSE118829** - Inamo J, Suzuki K, Takeshita M, Kondo Y et al. Molecular remission at T cell level in patients with rheumatoid arthritis. Sci Rep 2021 Aug 17;11(1):16691. PMID: 34404865
2. **GTRD:** an integrated view of transcription regulation. Kolmykov S, Yevshin I, Kulyashov M, Sharipov R, Kondrakhin Y, Makeev VJ, Kulakovskiy IV, Kel A, Kolpakov F Nucleic Acids Res. 2021 Jan 8;49(D1):D104-D111.
3. Kuijjer ML, Quackenbush J, Glass K (2019). "**lionessR:** single-sample network reconstruction in R." doi: 10.1101/582098, published on bioRxiv preprint server, https://www.biorxiv.org/content/10.1101/582098v1.
4. Souto-Carneiro, M.M.; Klika, K.D.; Abreu, M.T.; Meyer, A.P.; Saffrich, R.; Sandhoff, R.; Jennemann, R.; Kraus, F.V.; Tykocinski, L.; Eckstein, V.; et al. Effect of Increased Lactate Dehydrogenase A Activity and Aerobic Glycolysis on the Proinflammatory Profile of Autoimmune **CD8+ T Cells in Rheumatoid Arthritis.** Arthritis Rheumatol 2020, 72, 2050–2064, doi:10.1002/art.41420.
5. Weyand, C.M.; Goronzy, J.J. The Immunology of Rheumatoid Arthritis. Nat Immunol 2021, 22, 10–18, doi:10.1038/s41590-020-00816-x.

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