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

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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 downregulated. 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.

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


Acknowledgement

The authors would like to thank **Institute of Bioinformatics and Applied Biotechnology (IBAB)** for providing the facilities for performing this work. This work was also supported by the **Department of IT, BT and S&T of the Government of Karnataka**. Shilpa Harshan is a PhD student registered under **Manipal Academy of Higher Education**.