Hyperactive chemotaxis contributes to anti-TNFα treatment resistance in inflammatory bowel disease

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STUDY AIMS

Anti-tumour necrosis factor-alpha (anti-TNFα) treatment has up to 30% unresponsive rate for inflammatory bowel disease (IBD) patients.

Identifying potential molecular pathways may lead us to uncover treatment non-responder, improve the treatment management and prevent the disease progression.

METHOD

NCBI GEO database

Dataset Searching
[Keywords including: IBD, anti-TNFα]

5 eligable transcripomic datasets

Data normalisation, Batch effects Correction

1

Immune Environment Scores Evalusation (ESTIMATE, xCELL)

2

5 *In silico* flow cytometry (CIBERSRT, xCELL, EPIC, MCP-Counter, DTEIC)

Pathways analysis (MetaScape)

3

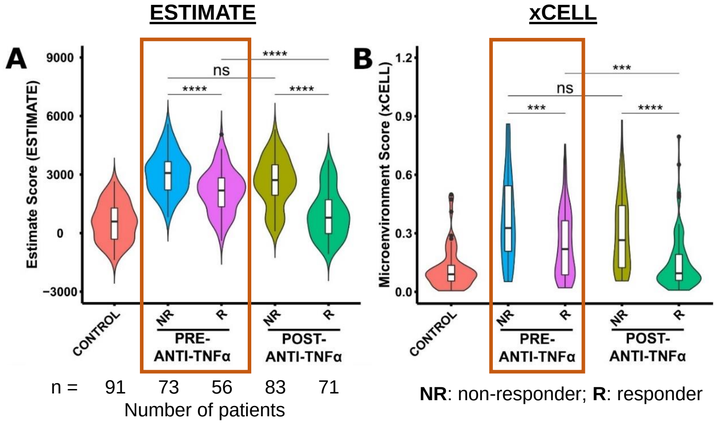
Raw RNA-Seq Data, GSE145918

Normalisation & log2+1 transformation

Mean expression level (across samples) of genes matching indicated GO term

RESULTS

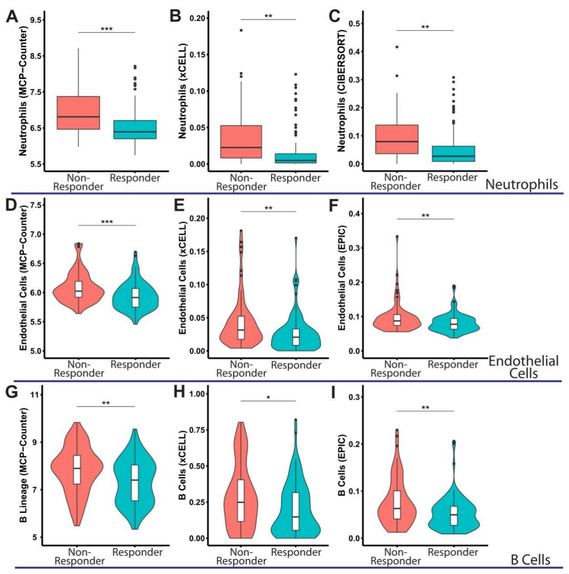
1. Immune-microenvironment scores evaluation



NR: non-responder; **R**: responder

Initial evaluation on immune microenvironment scores via (**A**) ESTIMATE and (**B**) xCELL algorithms identified anti-TNFα treatment non-responders are significantly higher compared to the responders on the base-line level.

2. High Neutrophils, Endothelial and B cells in pre-treatment non-responder

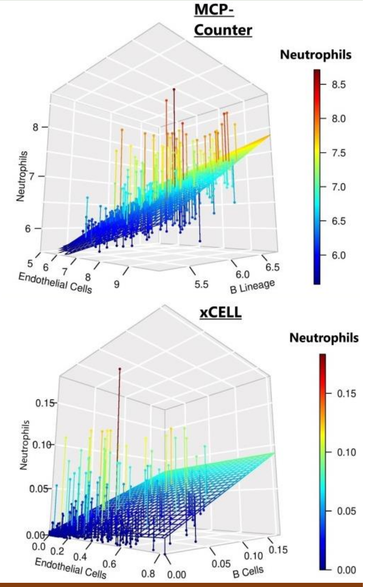


Left:

Immune cells population evaluated in five *in silico* flow cytometry. (**A-C**) neutrophils, (**D-F**) endothelial cells and (**G-I**) B cells can be recognised in three out of five algorithms and the cells populations are higher on baseline anti-TNFα non-responders compared to responders.

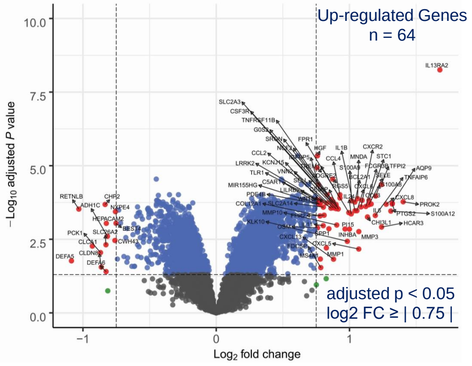
Right:

MCP-Counter and xCELL are enable to calculate all the targeted immune cells and have positive correlations with each other.



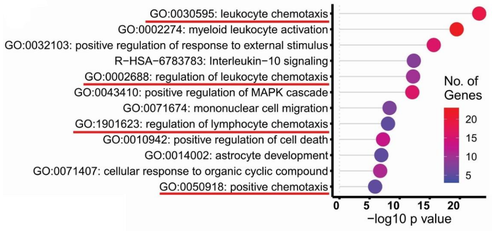
3. Chemotaxis involves in anti-TNFα resistance

Responder vs Non-Responder (Pre-treatment)



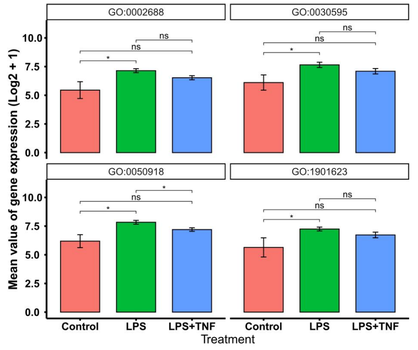
With the threshold of adjusted p-value < 0.05 and absolute log 2-fold change ≥ 0.75, a total of 64 up-regulated genes were identified.

Enrichment Pathway Analysis The top 12 pathways



The 64 up-regulated genes were utilised for Metascape – an enrichment pathway analysis tool based on the previously pre-defined gene sets. GO terms related to the chemotaxis-related pathways are underlined and further verified in neutrophils from the experimental animal model. GO: Gene Ontology.

Matched GO terms in chemotaxis verified in neutrophils expression data

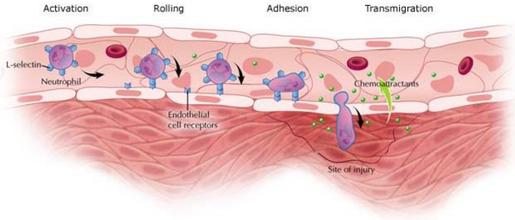


The GO terms related to chemotaxis are statistically higher in LPS-exposed neutrophils, three out of the four GO terms do not have significant reduction in the anti-TNFα treated group. LPS: Lipopolysaccharide.

CONCLUSIONS

Combination with the finding of immune cell deconvolution, enrichment pathway analysis and neutrophils from the experimental animal model. Hyperactive chemotaxis contributes to anti-TNFα treatment resistance in IBD patients.

Immune cells chemotaxis



PREPRINT AND R CODE

- ❑ biorxiv.org/content/10.1101/2021.08.15.456400v1
- ❑ github.com/paytonyau/anti-TNF-resistance