P035 TNF-driven pathways are increased at baseline in Crohn's disease patients not responding to infliximab

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Background

Anti-TNF therapy (infliximab, IFX) is effective for treating Crohn's Disease (CD) but 15–25% of patients fail to respond.

Pathophysiological understanding of primary response (R) and non-response (NR) to IFX might help to predict who will benefit most from it. Additionally, it may highlight other potential therapeutic targets in non-responders.

Methods

Inflamed colonic mucosal biopsies from 17 CD patients (11 R and 6 NR, median age 31.8 years) before first IFX infusion were studied. Total RNA was analysed for whole genome expression via Affymetrix Human Genome U133 Plus 2.0 Arrays, followed by a Weighted Gene Co-expression Network Analysis [1]. A false discovery rate <0.1 was considered biologically significant. Gene set enrichment and upstream regulation analyses were performed with Ingenuity Pathway Analysis. Mann-Whitney U-test or Fisher's exact test were used, when appropriate.

Results

Network analysis identified 70 gene clusters of which 4 (including 2179 probe sets) were correlated with (N)R to IFX. Consensus clustering using these identified probe sets perfectly discriminated R from NR. Although disease activity and CRP were not significantly different between R and NR at baseline, pathway analysis showed increased (a)granulocyte adhesion and diapedesis, TREM-1 signalling, IL-6 signalling, inhibition of matrix metalloproteases and NF-kB signalling at baseline in NR. Upstream regulation analysis identified TNF and TGF βb 1 as the strongest upstream regulators. Also TREM-1 was identified as a potential upstream regulator. Interestingly, the previously identified top 5 differentially expressed genes between IFX R and NR [2], are regulated by TNF and/or TGF βb 1 and TREM-1. Colonic mRNA levels of TNF, TGF βb 1 and TREM-1 showed a significantly higher expression in IFX NR vs R. Finally, we hypothesized that NR with increased TNF-driven pathways at baseline may need more TNF-blockade. We therefore retrospectively reviewed the need for dose escalation within the first year after IFX induction and found that 50.0% of NR received dose escalation, all successfully leading to R.

Conclusion

At baseline several inflammatory pathways differ between IFX R and NR. TNF was the strongest predicted upstream regulator and colonic TNF mRNA levels were significantly higher in IFX NR, suggesting that local cytokine production is (partially) driving these upregulated pathways. These patients may benefit from a higher dose of anti-TNF to neutralise gut inflammation. Additionally, therapy directed against TREM1, a triggering receptor expressed on myeloid cells, may also be a potential treatment strategy in these patients.

References:

[1] Langfelder P. et al. (2008), WGCNA: an R package for weighted correlation network analysis, BMC Bioinformatics

[2] Arijs I et al. (2010), Predictive value of epithelial gene expression profiles for response to infliximab in Crohn's disease, Inflamm Bowel Dis