Cytokine responsive transcriptional networks in inflammatory bowel disease

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Background: Interactions between the immune system and the intestinal epithelium play an important role in the pathogenesis of chronic immune mediated inflammatory diseases, including inflammatory bowel disease (IBD). In IBD, debilitating symptoms and complications including abscesses and cancer are associated with aberrant cytokine production and resulting intestinal epithelial damage. Despite the advent of biological therapies targeting key pathogenic cytokines, like tumour necrosis α (TNF), only 18% of IBD patients will achieve complete disease control and mucosal healing. Here, we provide new insights into the epithelial response to cytokines using network analysis of transcriptomics data from colonic organoids (colonoïds).

Methods: We generated an atlas of the transcriptomic effects of cytokines by treating human-derived colonoïds with IFNg, IL13, IL9, IL17A and TNF independently. By integrating the observed transcriptional changes with previously published signalling and regulatory interactions, we generated causal networks to elucidate the effect of cytokine cues on epithelial cells. These networks comprised experimentally verified protein–protein and transcription factor (TF)–target gene interactions, forming signalling pathways linking cytokines to TFs and from TFs to differentially expressed genes.

Results: With this analysis, we identified previously unrecognised levels of shared and distinct transcriptional regulation of colonic epithelial function by different cytokines. While IL9 had a negligible impact on the transcriptome, the transcripts with differential expression induced by IFNg, IL13, IL17A or TNF were consistent with their recognised function in other tissues. IFNg and TNF exhibited similar magnitude and directional effects on key immune pathways while IL13 had the opposite effect. Using a network approach, we found that regulatory effects of cytokines are primarily transduced through unique signalling routes, some of which converge on the same key transcription factors; CEBPA, E2F1, E2F2, ETS1, FOS, IRF1 and MAZ. We observed independent regulatory mechanisms of the different cytokines as well as complementarity in the epithelial responses regulated by different canonical cytokines.

Conclusion: The generated cytokine transcriptional atlas provides a unique insight into the immune-epithelial interactome by allowing the identification of shared and distinct transcriptional pathways across different types of immunity at the mucosal barrier. In addition, it provides the unique opportunity to study cytokine responses in the context of human disease and generate novel hypotheses.

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The pharmacologic inhibition of store-operated calcium entry pathway in inflammatory bowel disease

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Background: Store-operated calcium entry (SOCE) represents the major calcium influx pathway in T cells which not only controls the activation and function of lymphocytes, but which also has been implicated in the metabolic homeostasis and survival of murine CD4+ and CD8+ T cells. Conditional knockout mice, in which SOCE signalling components are deleted in T cells, revealed that SOCE is required for the induction of intestinal inflammation in mouse models of colitis. However, the effects of SOCE inhibition have not been studied in inflammatory bowel disease (IBD) and it remains elusive, which immune cell subset is affected by the pharmaceutical blockade of SOCE. We therefore aim to investigate the effects of SOCE inhibitor BTP-2 on functions and metabolic homeostasis of human lymphocytes isolated from IBD patients.

Methods: PBMC and/or lamina propria lymphocytes were isolated from colitis patients undergoing colon resection and mass cytometry served in order to evaluate the cytokine production and activation of B, T, NK as well as myeloid cells. Additionally, Ca2+ influx measurement and Seahorse analyses were performed in order to assess the metabolic status of immune cell subsets after SOCE inhibition.

Results: Data on B, T, NK, myeloid cells and neutrophils isolated from peripheral blood or colon lamina propria revealed that