

Host-microbial crosstalk in the pathogenesis of inflammation and cancer in Primary Sclerosing Cholangitis (PSC)

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Background

Distinct inflammatory responses have been involved in Primary sclerosing cholangitis-inflammatory bowel disease (PSC-IBD) and dysbiosis has been observed supporting a role for the microbiome in the pathogenesis of disease.

We aimed to: 1) assess host-microbial functions in PSC-IBD 2) evaluate whether PSC-IBD-associated pathways affect epithelial transformation.

Methods

Biopsies and mucosal brushings from colon and terminal ileum were collected from patients with PSC-IBD, ulcerative colitis without PSC (UC) and healthy controls (HC). 3'RNA sequencing was performed to analyse intestinal transcriptomes, with 16S rRNA sequencing to characterise the adherent microbiome.

Colonic crypts were isolated from biopsies, seeded onto basement membrane extract and cultured in media containing growth factors to develop organoids. Organoids were stimulated with cytokines for 24 hours and markers of cytokine downstream pathways, stemness and pluripotency were analysed by qPCR.

Results

The presence of a distinct transcriptomic profile in the caecal biopsies of patients with PSC-IBD compared to UC and HC were identified, with enrichment of pathways associated with cytokine signalling, such as IL22 and TGFbeta (Figure 1, A). Best add more data to Results - perhaps give % increase relative to controls, to help interpret the figure. Where is fig 1A? Only B and C in my version.

We successfully cultured primary intestinal organoids from both groups of patients and HC (Fig. 1, B). Stimulation with IL22 or IFNgamma resulted in *STAT1* induction. Interestingly, expression of the IL22 receptor, *IL22RA1*, was induced by IFNgamma stimulation in PSC-IBD derived organoids that also over-expressed *OLFM4*, a gene associated with pluripotency and early stages of neoplastic transformation (Fig.1, C).

Conclusions

A distinct transcriptomic profile in the colonic mucosa of patients with PSC-IBD show over-expression of pathways previously associated with IL22 and TGFbeta. Both cytokines have been implicated in cancer pathogenesis. PSC-IBD-associated Th1 responses may result in increased epithelial IL22 responsiveness. Higher expression of *OLFM4*, triggered by bacteria and IL22, suggest that microbial-driven IL22 responses may contribute to epithelial transformation.

Figure 1

