P56 – **Effects of microbial metabolites on human intestinal epithelium**

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The intestinal epithelium is the interface between the microbiota and the underlying host mucosa. Intrinsic genetic as well as acquired defects in the epithelium have been described in inflammatory bowel diseases (IBDs) including Crohn's disease (CD). Bacterial metabolites, such as short chain fatty acids (SCFAs), are known to exert homeostatic, anti-inflammatory and anti-tumoral effects. However, the effects of SCFAs in the context of intestinal inflammation and specifically in CD, have not been extensively addressed. Results from our group reveal that the epithelial organoid system is a good tool to explore the impact of bacterial metabolites on the human epithelium [1].

Our aim was to study the effect of fecal microbial SCFAs on the intestinal epithelium using organoid cultures from non-IBD controls and patients with CD.

SCFAs were extracted from fecal samples of non-IBD controls and active CD patients. The concentration of 13 SCFAs was measured in the derived fecal extracts (FEs) by HLPC. Organoid cultures, generated using biopsy samples from controls and CD patients, were incubated with fecal-SCFAs (1:50), or vehicle for 24 hours. Total RNA was isolated from organoid cultures and the expression of genes associated with proliferation and other epithelial signalling pathways was analysed by qPCR.

Despite the presence of active disease, fecal SCFA extracts from CD patients and controls showed comparable SCFA concentrations. Control FEs downregulated KI67, CXCL1 and CLDN2 but their effect was significantly lower in healthy compared to CD organoids. MT1X was significantly increased by control FEs, however the effect was lower in CD-derived organoids. Remarkably, SCFA from control FEs reduced IL8 transcripts in control organoids, and did not affect IL8 expression in CD organoids. SCFAs derived from active CD patients showed a decreased ability to induce MT1X and to decrease CXCL1 in epithelial organoids from controls.

Both the ability of the CD epithelium to respond to SCFAs as well as the composition of the SCFAs from active CD patients show changes that suggest an altered microbial-epithelial interaction in CD. While SCFAs have potent effects on the epithelium, other metabolites and bacterial products may also be critical. Our current experiments include studying the effects of supernatants from specific gut commensal and pathogenic bacteria on human organoid cultures.

[1]Dotti I et al. Gut 2017