Microbial Components Modify Intestinal Stem Cell Proliferation and Differentiation

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Background: Inflammatory bowel diseases result from genetic abnormalities that lead to an aggressive immune response to commensal bacteria. Central to this is disruption of the epithelial barrier. Despite this no current treatments target intestinal repair mechanisms. An important aspect of maintenance of the intestinal epithelium is its rapid turn over by the intestinal stem cells (ISC). We hypothesized that the activity of the ISC will be responsive to stimuli that reflect the efficacy of the intestinal barrier, in particular changes in the microbial composition of the lamina propria. Here we used colonic enteroids to investigate the effect of bacterial components on the proliferation and differentiation of the intestinal epithelium.

Methods: Human colonic enteroids grown from crypts obtained from transverse colon biopsies from healthy volunteers were maintained for 10d in the presence and absence of 20ng/ml lipopolysaccharide (LPS) or muramyl-dipeptide (MDP) then harvested. RNA and protein were analysed using microarray, qPCR, immunohistochemistry and western blotting.

Result: In the absence of bacterial components the resultant epithelium consisted mainly of columnar epithelial cells with basal nuclei, apical microvilli and well developed tight junctions. But, unlike the native colonic epithelium where ≈20% of the epithelial cells are goblet cells, there was a limited number of goblet cells (2.7±3%). However, with LPS, but not MDP, this increased to 20±3% (P<0.005). Associated with this was an increase in related genes (MUC2, TFF3 and KLF4) and MUC2 protein (P<0.005). Microarray analysis showed that LPS stimulated increases in the expression of genes associated with goblet cell differentiation (Atoh1, Clca1) and cell growth and regeneration (SMAD3, P15, CyclinD), while MDP increased the expression of genes associated with proliferation (Ki67, FOXM1).

Conclusions: These data indicate an important mechanism in the regulation of intestinal epithelial homeostasis via the crosstalk between intestinal stem cells and luminal bacteria. This model provides us with a means to study intestinal epithelial repair mechanisms and their potential dysregulation in IBD. This might lead ultimately to new therapeutic targets.