Characterising the active human gut microbiota in health and colorectal cancer

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Introduction Bacteria of the gut are associated with human health and gastrointestinal diseases including cancer. However, the microbial composition and contribution to disease is primarily derived from DNA analysis, representing their potential. The metatranscriptome, the expressed microbial genome, provides meaningful insights into bacterial activity and hence affords a new perspective on the contribution of the microbiota to health and disease. Using human faecal microbiota from colorectal cancer (CRC) and healthy controls, the signature of the active population contributing to health and disease can be established.

Methods High-throughput RNA sequencing of the faecal microbiota (CRC n=10 and control n=10) was analysed via Benjamini-Hochberg (FDR<0.05) adjusted Wald t-Tests.

Results Analysis of the active taxonomy, found, that of the 'core' 29 previously CRC-associated (based on DNA analysis) species, only 5 were differentially active, with activity of 3 species decreased and 2 increased. Interestingly, 24 species' activity remained unchanged in CRC, highlighting inconsistencies between abundance and activity. We also found that expression of specific genes critical for microbial mucus colonisation, permeability and modification is significantly greater during CRC. This strongly argues that the microbiota compromise the defensive capacity of the mucosa as the physical barrier during CRC. Intriguingly, expression of genes e.g. peroxidase, which control the level of reactive oxygen/nitrogen species (ROS) in the gut, was found to be reduced in CRC. This suggests that one of the central roles bacteria play during homeostasis, is to balance production and decomposition of ROS e.g. hydrogen peroxide in the gut, the failure of which, may prompt accumulation of genetic lesions. 16 butyrate-producing species known to modulate inflammation and barrier function e.g. Clostridium groups XIVa and IV, who have diminished abundance in CRC also exhibit lower activity. Furthermore, expression of the key butyrate synthesis gene, butyryl-CoA:acetate CoA-transferase was found to be under expressed during CRC. This argues depleted activity of butyrate-producing bacteria via the major butyrate production pathway is a true signature of CRC.

Conclusions We show that the taxonomy of active microbiota is not always consistent with abundances established by DNA sequencing, which appear to somewhat overestimate shifts in bacterial populations between homeostasis and disease. These novel data will light the path to targeting microbial gene expression as a means of next-generation therapeutic strategy to combat inflammatory diseases of the gut.

Reference