IN VITRO CELECOXIB SUPPLEMENTATION IMPACTS THE FUNCTIONAL CAPACITIES OF THE GUT MICROBIOTA

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Background
Alterations on inflammatory pathways lead to aberrant expression of cyclooxygenase-2 (COX-2) in colon carcinogenesis (CRC). The efficacy of COX inhibitors (coxibs) for successfully reducing CRC recurrence further confirmed the key role of COX-2. Alas, continuous COX-2 inhibition may increase the risk of a cardiovascular event. Currently, little information is available on how inter-individual variations in colon microbiota impact coxib disposition and overall celecoxib disposition.

Objectives
This project evaluated the effect of clinical concentrations of celecoxib on the in vitro colon microbiota. We determined the baseline microbiota activities and metabolic response, to reveal whether microbial drug metabolism impacts the conversion process.

Methods
We conducted in vitro batch culture experiments, assessing the potential of human faecal microbiota for metabolising celecoxib. Faecal slurries from four volunteers were supplied with 100 mg/ml of celecoxib and anaerobically incubated for 16h, to simulate the transit time of the proximal colon. Short-chain fatty acids (SCFAs) were considered benchmarks of gut microbial functionality and determined by gas chromatography. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) was used to determine celecoxib recovery. Total RNA was applied to perform qRT-PCR of the bacterial 16S rRNA gene and to evaluate the metabolically active population.

Conclusions
Our results indicate that celecoxib shifts in vitro fermentation, in a donor-dependent manner. Celecoxib significantly decreased total SCFA and butyrate ($P < 0.001$), but not copy number of 16S rRNA gene in all donors. Microbial-derived SCFA, such as butyrate, may fuel proliferation of cancer-initiated epithelial cells. This study will provide information about the microbiota interplay on the efficacy of colon-targeted coxibs.