Explants of Inflammatory Bowel Disease tissue in culture

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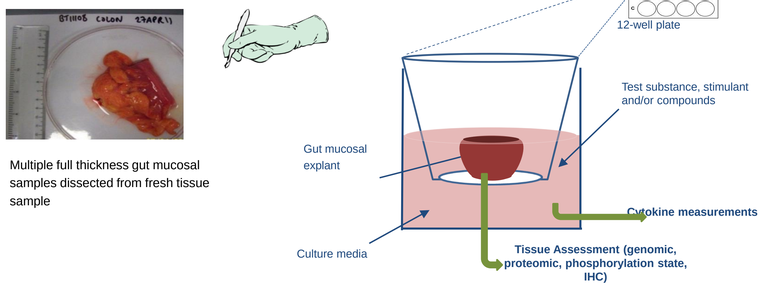
Introduction

Inflammatory bowel diseases (ulcerative colitis and Crohn's disease) are the focus of numerous companies seeking to find alternative treatments to standard of care therapies such as steroids and 5-ASA.

A major challenge to discovering new therapies has been the availability of disease-relevant *in vitro* or *ex vivo* models that would retain the disease phenotype.

Biopta has developed a test system that uses intact fresh mucosa from patients with IBD, allowing the application of test drugs and the comparison of effects with standard of care compounds.



Multiple full thickness gut mucosal samples dissected from fresh tissue sample

Multiple small biopsies of healthy or diseased mucosa are placed in culture for up to 24 hours. Test compounds can be added to the culture media, followed by measurement of biomarker release or changes in gene expression in the tissue.

Methods

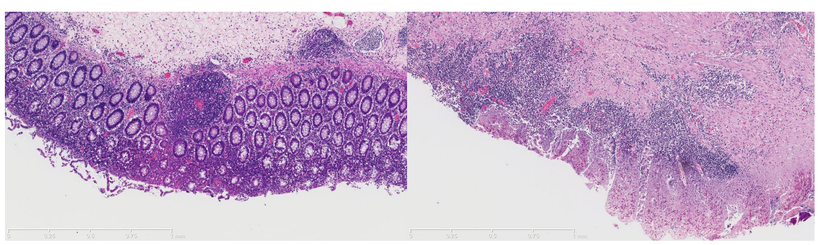
Human gastrointestinal tissues (healthy colon, UC or Crohn's disease) which were residual to surgery and donated with consent of the patient were transported to Biopta in Aqix solution. The tissue was then dissected into small biopsies of approximately 4-5 mm diameter and placed in Netwells™ partially submerged in culture medium (Figure 1), in a high oxygen environment (95% O2, 5% CO2) at 37 °C for up to 24 hours.

Tissues were challenged with test drugs, which were added directly to the culture media for various time periods in the presence or absence of lipopolysaccharide (LPS) or the vehicle used to carry the test drugs.

The production of cytokines was determined by the collection of samples of the culture media at various time points (typically 6 hours and 24 hours after the addition of the test drug). Cytokine levels were determined using a Bio-Rad Magpix instrument (Luminex platform).

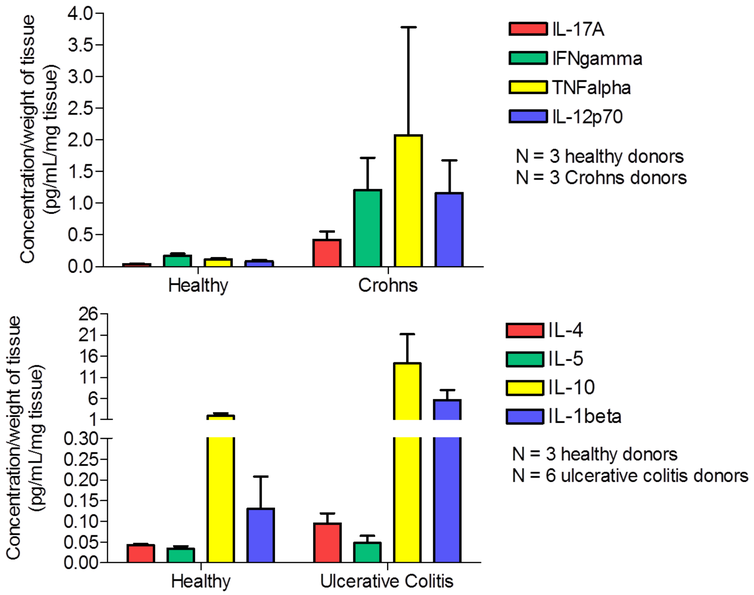
Results

Both UC and Crohn's disease tissues released higher levels of cytokines than healthy tissues. The cytokine profile observed in Crohns tissue followed the expected Th1/Th17 profile with elevated levels of various standard markers of this phenotype such as IL-17A, IFN-gamma, TNF-alpha and IL-12.

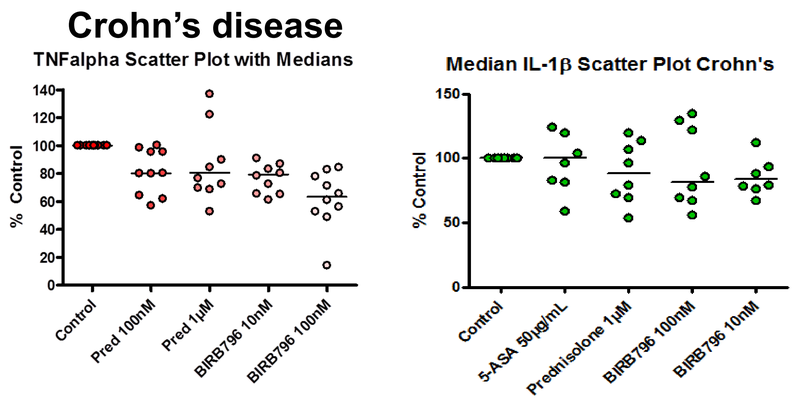


Crohn's Colon:
Shortened and widespread crypts, increased lamina propria cellularity and granuloma present

Ulcerative Colitis:
Crypt destruction, widespread mucosal erosion and severely thickened muscularis mucosa



The responses to a standard of care compound, prednisolone, and the MAP kinase inhibitor, BIRB796, were compared in Crohn's disease tissues. The results reflected the clinical responses to the compounds, with clear variation in the effectiveness of the drugs between patients (each dot represents the mean value from a single donor).



Conclusion

The *ex vivo* human tissue culture method is a valuable tool for assessment of test compound efficacy using disease relevant tissues. Such a model may also inform precision medicine strategies by reflecting the typical variation in drug response within the target patient population.