

ENDOCANNABINOID PATHWAYS IN INFLAMMATORY BOWEL DISEASE

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Background:

Inflammatory bowel disease (IBD) is a debilitating, poorly controlled disease affecting 1 in every 210 people in the UK. IBD remains a significant unmet medical need, with most patients ultimately submitting to surgery. The best current treatment agents, such as anti-TNF- α , therapies, come with black box warnings due to potential catastrophic infections and yet only benefit of subset of patients. My PhD research is focused on defining how the balance of pro- and anti-inflammatory lipids in the colon has become disrupted in IBD. Recent data has pointed to the role of hepoxilin A3 (HxA3) and the N-acylethanolamine (NAE) family of endocannabinoids in regulating the state of intestinal inflammation (Szabady et al, 2018, J Clin Invest; <https://doi.org/10.1172/JCI96817>).

Methods:

Levels of both pro-inflammatory HxA3 and anti-inflammatory NAEs were determined in human intestinal samples. Colonic scrapings were taken from ulcerative colitis and healthy patients. For ulcerative colitis patients, both disease affected and un-inflamed colonic samples were analysed. Organically soluble analytes were extracted by solvent extraction and separated using UPLC prior to analysis by electrospray ionisation QTOF MS.

Due to the inherent instability of HxA3, identification of its receptor has remained elusive. I am therefore using a novel protein internalisation method which aims to identify cell surface receptors that are endocytosed upon application of HxA3. The internalised proteins are then identified using mass spectrometry. This innovative method overcomes the major hurdle for baiting a receptor. An orthogonal approach using transmigration assays will validate findings.

Results:

Quantitation of the pro- and anti-inflammatory lipids in human intestinal samples was determined. The ability to measure and correlate HxA3 and NAEs levels with inflammatory status provides the first-ever possibility to monitor and understand the processes of remission and relapse in the inflammatory diseases related to these lipids. Preliminary data show higher levels of HxA3 in inflamed tissues, whilst levels of NAEs show a decrease.

Conclusions:

This research has multiple potential applications, from the development of safer and more effective drug treatments for IBD, to increasing the wider understanding of epithelial cell structure and function in health and disease, which is important for the delivery of pharmaceuticals across the intestinal barrier. Understanding the balance of HxA3 and NAEs lipid levels as they relate to inflammatory status will provide clinical hallmarks that could be used to identify new biomarkers for early diagnosis of IBD.