Investigating the interplay between the TNF superfamily factor 14/LIGHT and HIF in inflammatory fibroblasts

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Introduction: Intestinal inflammatory fibroblasts contribute to Inflammatory-Bowel-Disease (IBD) pathogenesis by mechanisms that are poorly understood. The tumor necrosis super family factor 14, also known as LIGHT, promotes inflammation in fibroblasts in other tissues such as lung and oesophagus. Here we test the role of LIGHT on intestinal fibroblast inflammatory responses and the impact of hydroxylase inhibition in this process.

Methods: The effect of LIGHT treatment in primary human colonic fibroblasts CCD-18Co (18Co) and intestinal epithelial cells (T84) was compared by flow cytometry and PCR. 18Co were treated with various hydroxylase inhibitors, stimulated with LIGHT and their inflammatory profile assessed by qPCR, flow cytometry, ELISA and Immunoblot-analysis.

Results: LIGHT induced CCL2, CXCL10 and IL34 gene expression, CCL2 protein secretion and surface expression of ICAM1 and VCAM1 in 18COs. A comparative analysis demonstrated that this response was absent in T84s, suggesting selective effects of LIGHT on the intestinal stroma. Hydroxylase inhibition with either DMOG or Roxadustat resulted in decreased LIGHT-mediated CXCL10, CCL2 and IL34 gene expression at 8h post-stimulation in 18Co. Conversely, LIGHT depleted the stabilization of HIF-1α in 18Co in the presence of hydroxylase inhibition suggesting a reciprocal interaction between LIGHT and HIF signalling pathways. LIGHT-induced cleavage of p100 to trigger non-canonical NF-κB is one of the best characterized LIGHT-mediated inflammatory signalling pathways. DMOG did not prevent LIGHT-mediated p100 cleavage, suggesting that the anti-inflammatory effects of hydroxylase inhibition are mediated by an alternative LIGHT-induced pathway.

Conclusions: Our current studies show that LIGHT is a mediator of colonic inflammatory fibroblast differentiation. Hydroxylase inhibitors show selective effects on the LIGHT-driven response in fibroblasts via a mechanism independent of non-canonical NF-κB signalling.

This project is funded by an SFI/IRC Pathway award (21/PATH-S/9621) to MCM.