Regulation of RELMβ expression by Intestinal Guanylate Cyclase C

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Background: Today over two billion people are infected with helminth worms. Helminths infect the intestine and cause delayed physical and mental development. RELMβ is a goblet cell-derived anti-parasitic protein that is induced during worm infection and is required for expulsion of lumen dwelling worms. Guanylate Cyclase C (GC-C) is a transmembrane receptor located in intestinal epithelial cells and may be important in gastrointestinal responses to inflammation and injury. GC-C knockout mice produce less RELMβ basally as compared to wildtype mice and fail to induce RELMβ in models of intestinal injury. It is not known whether poor RELMβ expression in GC-C knockout mice results from a change in mucosal cytokine profile or a defect intrinsic to goblet cells themselves. Here, we utilize *in vitro* models to focus on the role of GC-C signaling in cytokine-induced RELMβ expression. We hypothesize that blockade of GC-C signaling will blunt expression of RELMβ.
Methods: A goblet cell-like human cell line (HT-29-18-N2) was infected with a lentivirus that expresses an inactive, dominant negative GC-C mutant. In some studies, GC-C signaling was also blocked using an antagonistic nucleotide analog (Rp-8-pCPT-cGMPs). Cells were stimulated with IL-13, a cytokine which induces goblet cell differentiation and RELMβ in a manner similar to that which occurs during worm infection. Realtime RT-PCR was used to measure expression of RELMβ and other goblet cell-specific genes. Goblet cells in wildtype and GC-C null mice were stained with alcian blue and quantitated.
Results: Although more work is necessary to confirm our preliminary studies, realtime RT-PCR analysis of RELMβ expression in IL-13-stimulated HT29-18-N2 cells indicates that GC-C does not affect expression of this gene *in vitro*. We did note, however, that GC-C knockout mice showed a 20-25% reduction in goblet cells in the small intestine as compared to wildtype mice.
Conclusion: We conclude that GC-C signaling does not play a significant role in induction of RELMβ in response to IL-13. Studies aimed at directly investigating the role of GC-C in RELMβ expression in the context of helminth infection are ongoing.