Title: The Role of Guanylyl Cyclase C During Intestinal Adaptation.

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Introduction: Following a proximal small bowel resection (SBR), the intestine adapts by increased crypt depth and villus height compared to sham operated mice (transection and reanastomosis only). The epidermal growth factor receptor (EGFR) is a known mediator of intestinal adaptation and results in activation of the GTPase Rac. This activates PAK (p21-activated protein kinase) which may activate guanylyl cyclases. We sought to determine whether guanylyl cyclase C (GC-C) was activated by PAK and its roles in intestinal adaptation.
Methods: GC-C knockout and wild type mice, both maintained on a liquid diet, underwent a SBR or a sham operation. Mice were then sacrificed at different time periods, 1, 2, or 3 days. The small intestine was harvested and ileum and jejunum samples were analyzed via western blot and histological preparation.
Results: GC-C KO mice exhibited an obstructed phenotype at 2 and 3 days post-SBR (16/16) whereas GC-C wildtype mice did not (0/3) ($p<0.001$). Even sham operated GC-C KO animals demonstrated a partial obstruction (9/11) whereas sham operated WT animals did not (0/3) ($p=.03$). At 1-day post-SBR, the small intestines of both genotyopes ($n = 2$) were similarly distended proximal to the anastomosis site. Based on histological inspection, the same level of inflammatory infiltrate was present in both WT and KO SBR mice at all time points. There were no obvious differences in architecture in the mucosa or submucosa of WT vs KO SBR animals although the tissue from the obstructed animals was very friable.
Conclusions: Unexpected obstruction of KO mice has prevented proper analysis of whether GC-C mediates intestinal adaptation. We are currently evaluating potential etiologies for the obstructed phenotype we observed. Obstruction following SBR in the absence of GC-C suggests that GC-C regulates a critical pathway involved in healing from surgical wounding in the intestine.