

Title: *Development of a Murine Model to Investigate the Influence of Chronic Colitis on Colonic Adenocarcinoma Tumor Growth*

Program of Study: Osteopathic Medicine

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Abstract:

Background. Colorectal cancer is the third most commonly diagnosed cancer, as well as the third leading cause of cancer mortality in the United States. Ulcerative colitis (UC), a chronic inflammatory disease of the colon, has been shown to increase the incidence of colorectal cancer. Approximately 20% of UC patients are projected to develop colorectal carcinoma during their life-time. Chronic colitis increases the likelihood of epithelial dysplasia and adenocarcinoma of the colon.

Objective. Our objective is to integrate two mechanistic disease models into a single murine model in which to investigate the effects of inflammation on colorectal cancer development. We hypothesize that our new interactive murine model will allow us to investigate the potential interactive effects of chronic colitis on colonic adenocarcinoma tumor characteristics. Furthermore, we hypothesize that the colitic inflammatory milieu will augment tumor growth, potentiate neoangiogenesis, alter leukocytic infiltrates and modulate enteric neuroplasticity.

Methods. The colitis component of the colitis/cancer model was constructed using C57Bl/6 that were fed water or dextran sodium sulfate (DSS) 3% until sacrifice on day 10. Colons were grossly and histologically inspected (N=5,5). Spatial distribution of neutrophil infiltrates were quantified using a novel lamina propria (LP)/muscularis externa (ME) whole-mount

preparation (N=6). Colonic tissue and serum cytokines were determined using a MAGPIX cytokine panel (N=6,6). The cancer component of the colitis/cancer model was constructed by the colonic submucosal injection of a C57Bl/6 adenocarcinoma cell line (MC38 – 50,000 cells). Spatial distribution of neutrophilic infiltrates were quantified using the lamina propria/muscularis externa (ME) whole-mount preparation. On-going experiments will characterize tumor development, including: tumor growth, neoangiogenesis, molecular inflammatory responses and recruited leukocytic phenotyping.

Results. At sacrifice, colonic DSS histology exhibited hemorrhagic mucosal sloughing. Analysis of neutrophilic infiltrates within the lamina propria demonstrated DSS-induced dense cellular infiltrates that were clustered around the lamina propria venules (cntrl=162.0±6.01 vs. DSS=48.4±8.05 luminosity, 100X field). DSS colonic ME whole-mounts had a mild significant increased presence of neutrophils compared to controls (cntrl=1.5±0.97 vs. DSS=24.2±1.3, 100X field). Immune analysis of the conditioned media of the organ cultured LP/ME tissue demonstrated significant increases in VEGF, IL-10, MIP-1 α & GM-CSF compared to control. Serum cytokines also showed a systemic inflammatory response (VEGF, IL-6 & MCP-1). In regards to the colon cancer model, two weeks after MC38 adenocarcinoma injection into the colonic submucosal space, a discrete neoplastic growth was microscopically visualized within the lamina propria. Interestingly, an intense myeloperoxidase-positive neutrophilic and monocytic inflammatory response enveloped the focal neoplasm. Additionally, a diffuse transmural myeloperoxidase-positive neutrophilic inflammatory response was observed extending beyond the neoplasm.

Conclusion. We have successfully developed individual models of colitis and colon cancer, which can be easily combined to produce a unique and novel interactive colitis/cancer model. We propose that the novel murine colitis/cancer model will allow us to gather crucial data regarding the interactive colitic tumor microenvironment. Pending the results of the study, targeting specific inflammatory mediators could be used as a potential therapeutic intervention for cancer prevention and treatment.