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Modeling the impact of inflammatory bowel disease on prostate cancer in mice

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Background

- Recent epidemiological data has implicated inflammatory bowel disease (IBD) as a risk factor for clinically significant prostate cancer (PC).
- A key driver of malignant transformation may include chronic inflammation, however, the effects of gut inflammation on the prostate are unknown.

Objectives

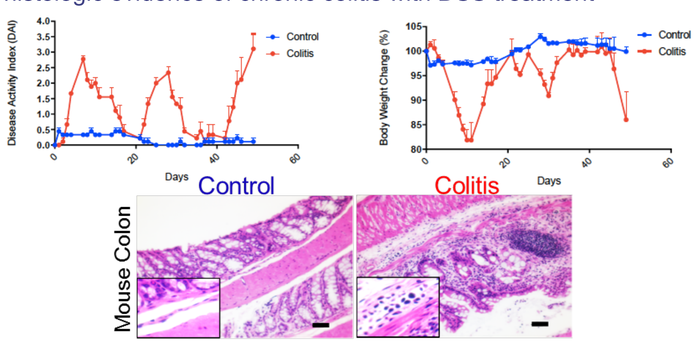
- To determine whether gut inflammation leads to changes in the inflammatory milieu and pro-oncogenic signaling in the prostate of wild-type mice.

Methods

- Chronic colitis was induced by administering C57BL/6 mice with 3 cycles of 3% dextran-sodium sulfate (DSS) – treated water for 7 days followed by 14 days of rest.
- Mice were assessed daily for weight loss, stool consistency, and hematochezia and sacrificed for immunophenotyping following the third cycle of DSS.
- Prostatic leukocyte (CD45+) infiltration and epithelial cellular proliferation (Ki67+) were assessed by immunostaining. Western blotting was used to assess prostatic molecular pathway activation, reactive oxygen species, and DNA damage. Prostatic cytokine profiling was performed using multiplex ELISA and validated by immunostaining.
- Statistical significance was assessed using a two-tailed students t-test with Welch's correction where appropriate

Figure 1. Mouse Model

Figure 2. Colitis mice demonstrated bloody diarrhea, weight loss, and histologic evidence of chronic colitis with DSS treatment



Results

- Colitis (DSS-treated) mice exhibited bloody diarrhea and weight loss with progression of colitis. Histologic analysis of the colon demonstrated epithelial erosion and infiltration of granulocytes into submucosa.
- In the prostate, colitis mice had more CD45+ leukocyte infiltration as well as increased levels of pro-inflammatory cytokines known to drive tumorigenesis—TIMP1, CCL5, CXCL1.
- Colitis had evidence of downstream activated AKT and NF-kB signaling as well
- Lastly, colitis mice had elevated reactive oxygen species, DNA damage, and reduced epithelial proliferation (i.e. cell cycle senescence).

Figure 3. Chronic colitis leads to prostatic CD45+ leukocyte infiltration

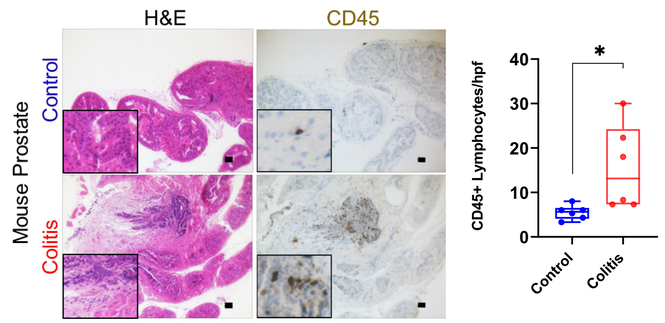


Figure 4. Chronic colitis upregulates prostatic expression of pro-inflammatory cytokines: TIMP1, CCL5, CXCL1

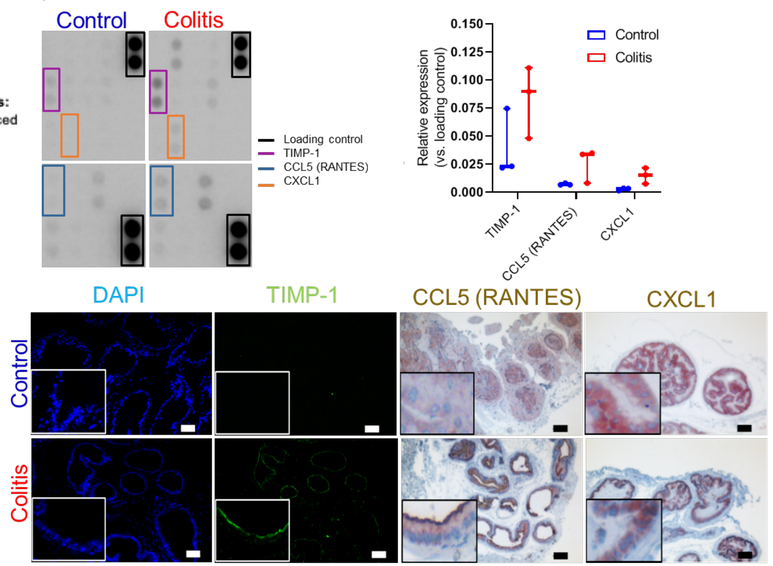


Figure 5. Chronic colitis upregulates inflammatory-associated pro-oncogenic signaling

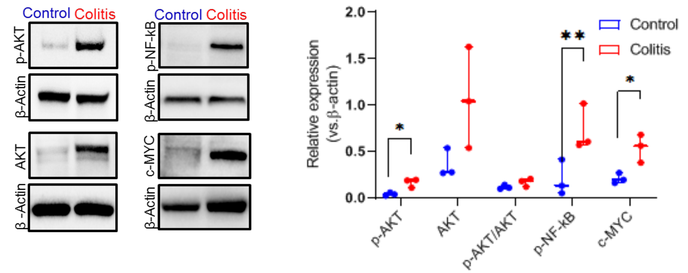
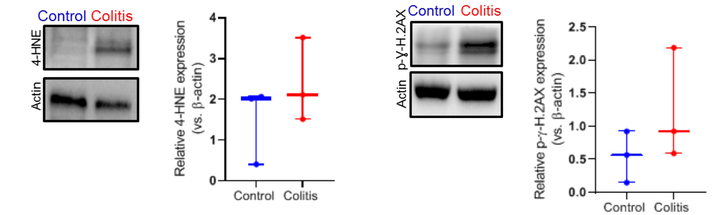
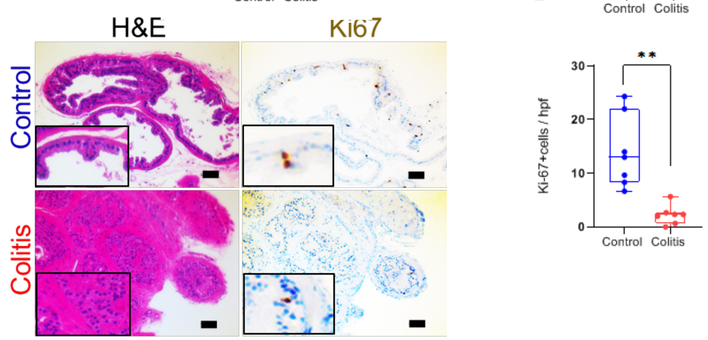


Figure 6. Chronic colitis leads to prostatic, reactive oxygen species (4-HNE), DNA damage (p-ɣ-H.2AX) and cell cycle senescence (Ki67 reduction)—a characteristic pre-neoplastic phenotype in inflammation mediated carcinogenesis





Conclusions and Limitations

- Induction of chronic colitis in wild-type mice leads to greater prostatic prostatic inflammatory infiltrate, activates pro-oncogenic AKT and NF-kB signaling pathways, and leads to prostatic genomic instability/cell cycle senescence.
- While these findings may partially explain the pathogenesis of IBD-associated prostate cancers, they are limited by factors inherent to our murine model and require further validation.