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PLoS One. 2013 Nov 11;8(11):e79182. doi: 10.1371/journal.pone.0079182. eCollection 2013.

Characterization of dextran sodium sulfate-induced inflammation and colonic tumorigenesis in Smad3(-/-) mice with dysregulated TGFβ.

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Abstract

There are few mouse models that adequately mimic large bowel cancer in humans or the gastrointestinal inflammation which frequently precedes it. Dextran sodium sulphate (DSS)-induces colitis in many animal models and has been used in combination with the carcinogen azoxymethane (AOM) to induce cancer in mice. Smad3(-/-) mice are deficient in the transforming growth factor beta (TGFβ) signaling molecule, SMAD3, resulting in dysregulation of the cellular pathway most commonly affected in human colorectal cancer, and develop inflammation-associated colon cancer. Previous studies have shown a requirement for a bacterial trigger for the colitis and colon cancer phenotype in Smad3(-/-) mice. Studies presented here in Smad3(-/-) mice detail disease induction with DSS, without the use of AOM, and show a) Smad3(-/-) mice develop a spectrum of lesions ranging from acute and chronic colitis, crypt herniation, repair, dysplasia, adenomatous polyps, disseminated peritoneal adenomucinosis, adenocarcinoma, mucinous adenocarcinoma (MAC) and squamous metaplasia; b) the colon lesions have variable galactin-3 (Mac2) staining c) increased DSS concentration and duration of exposure leads to increased severity of colonic lesions; d) heterozygosity of SMAD3 does not confer increased susceptibility to DSS-induced disease and e) disease is partially controlled by the presence of T and B cells as Smad3(-/-) Rag2(-/-) double knock out (DKO) mice develop a more severe disease phenotype. DSS-induced disease in Smad3(-/-) mice may be a useful animal model to study not only inflammation-driven MAC but other human diseases such as colitis cystica profunda (CCP) and pseudomyxomatous peritonei (PMP).

PMID: 24244446 [PubMed - in process] PMCID: PMC3823566 **Free PMC Article**

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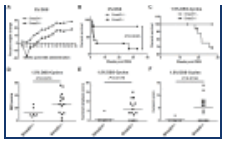
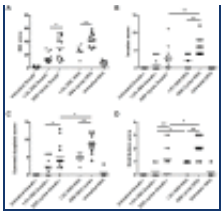
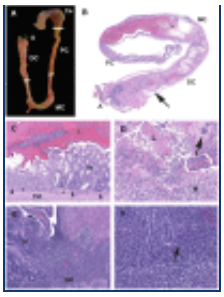
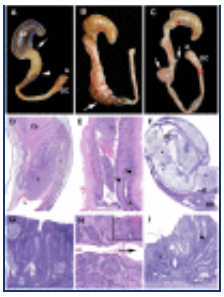
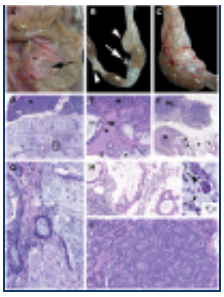
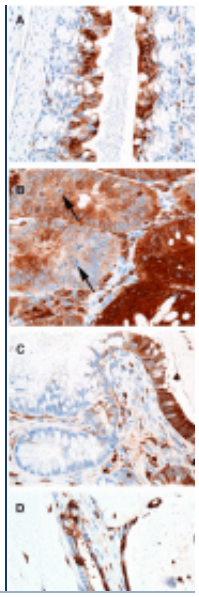

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