VACCINE TARGETING OF THE TUMOR-ASSOCIATED ANTIGEN BRACHYURY REDUCES DEVELOPMENT OF COLITIS-INDUCED COLORECTAL LESIONS IN THE APCMIN/+ MOUSE MODEL

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Background Colorectal cancer (CRC) poses a significant public health risk as the third most diagnosed cancer globally. While most CRC cases arise through sporadic somatic mutations, a significant proportion have a hereditary component, and approximately 5% of CRC cases are directly attributed to hereditary cancer syndromes. One such syndrome is Familial Adenomatous Polyposis (FAP) characterized by mutations in the tumor suppressor gene adenomatous polyposis coli (APC), which result in the development of numerous colorectal adenomas and an almost 100% risk of developing CRC. Vaccine approaches aimed at targeting antigens found in these pre-malignant adenoma lesions are being investigated in the clinic with the goal of preventing the onset of CRC.

Methods The APCMIN/+ mouse model, which harbors a heterozygous nonsense germline mutation in the APC gene leading to the development of numerous adenomas in the small intestine, was used in this study. Formation of colonic lesions was induced in APCMIN/+ mice through exposure to the colitis-inducing agent, dextran sodium sulfate (DSS), which resulted in the development of multiple, large adenomas and isolated carcinomas in the colon. Lesions were extensively characterized via flow cytometry analysis, multiplex immunofluorescence staining, RNA in situ analysis, and single cell RNAseq analysis. APC-DSS mice were treated with an adenoviral vaccine (Ad-brachyury) encoding the full sequence of the murine brachyury protein.

Results Analysis of APC-DSS colonic lesions demonstrated a marked upregulation of the embryonic transcription factor brachyury, a tumor-associated antigen that is being investigated in the clinic as a target for cancer vaccine approaches. Expression of brachyury was co-localized to markers of intestinal stem cells, including LGR5, with brachyuryPOS colonic cells also expressing features of epithelial-mesenchymal plasticity. Based on these observations, APC-DSS mice were vaccinated weekly with an Ad-brachyury or control vaccine starting prior to the administration of DSS. Vaccination with Ad-brachyury significantly increased the number of splenic brachyury-specific T cells, increased the number of granzyme BPOS/CD8POS T cells in spleens and tumors, and decreased the number of colonic lesions compared to mice vaccinated with Ad-control or untreated mice.

Conclusions Overall, this study highlights the efficacy of a vaccine approach targeting a tumor-associated antigen to reduce colitis-induced colorectal lesion development. Studies are currently ongoing and planned to identify candidate immunotherapies or other anti-cancer agents to combine with this vaccination approach.

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