Title:	Characterization of Transgenic Knock-in Models of Colorectal Cancer and Evaluating Therapeutic Agents in Knockout Models in Preclinical Settings.
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Abstract:	Colorectal cancer (CRC) has been long-observed as a vicious form of tumorigenesis, with over 1.9 million new cases and 900000 deaths, as estimated in 2022. It advances through a gradual multistep process caused by progressive accumulation of genetic and epigenetic mutations in the normal colorectal epithelium. Hyperactivation of Wnt/β-catenin signalling caused by the inactivation of Adenomatous polyposis coli (APC) gene has been heavily implicated as one of the major events in the initiation and progression of colonic carcinogenesis. Wnt/β-catenin signalling deregulation being one of the leading causes of colorectal cancer, effective targeting of the pathway offers hope for the emergence of a wide range of therapeutic strategies. To explore the Wnt deregulators that are involved in the onset and progression of CRC, the lab performed a microarray analysis on APC fl/fl conditional knockout mice, which revealed the overexpression of several genes like EphB4, c-Myc, CITED-1, MMPs, etc. The primary objective of the project is to study the role of CITED-1 in the initiation and progression of CRC using two transgenic knock-in murine models generated previously by the lab, one with CITED- 1 gene under a constitutive promoter, villin promoter, and the other with CITED-1 gene under an inducible promoter, CYP1A1 promoter. Characterization studies were carried out on these models using differential staining methods and immunohistochemistry analysis. To explore the morphological changes in the intestine induced by the CITED-1 gene, immunohistochemical analysis of Ki67 and BrdU was carried out. Further, characterization was carried out using differential staining methods like Alcian blue, and Grimelius staining. The results of these experiments revealed morphological changes along with an increase in the proliferation of different intestinal cells like goblet cells and enteroendocrine cells, in the transgenic models as compared to the wild type. The immuno-histochemical analysis of β-catenin, c-Myc, CITED-1, and lysozyme confirmed the role of CITED-1 in the deregulation of the Wnt/β-catenin signalling pathway. Furthermore, the possibilities of using an RNAi based drug (nanoconjugate of Curcumin-chitosan coupled with Ephb4 shRNA encapsulated by eudragit) as a novel therapeutic regimen for colorectal cancer in APC fl/fl conditional knockout mice are being explored. Additionally, extracts from E. hirta were subjected to evaluation for its anti- cancer properties. Keywords: Colorectal cancer, Wnt/β-catenin signaling, transgenic murine models, Curcumin nanoconjugate, phytochemical.
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