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Literature Review of Different Genes Involved in Colorectal Cancer

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Abstract

Cancer is characterized by pervasive epigenetic alterations with enhancer dysfunction orchestrating the aberrant cancer transcriptional programs and transcriptional dependencies. Colorectal cancer (CRC) is one of the leading cancers worldwide, accounting for high morbidity and mortality. The global incidence of early-onset colorectal cancer (EO-CRC) is rapidly rising. However, the reason for this rise in incidence as well as the genomic characteristics of EO-CRC remains largely unknown. The mechanisms governing tumor growth and metastasis in CRC require detailed investigation. This work indicates a common layer of YAP/TAZ-fueled enhancer reprogramming that is key for the cancer cell state and can be exploited for the development of improved therapeutic avenues. Interleukin (IL)-11 is a member of the IL-6 family of cytokines and is involved in multiple cellular responses, including tumor development. However, the origin and functions of IL-11- producing (IL11+) cells are not fully understood. To characterize IL-11+ cells in vivo, we generate Il11 reporter mice. IL-11+ cells appear in the colon in murine tumor and acute colitis models. Il11ra1 or Il11 deletion attenuates the development of colitis-associated colorectal cancer. The aberrant gain of DNA methylation at CpG islands is frequently observed in colorectal tumours and may silence the expression of tumour suppressors such as MLH1. Current models propose that these CpG islands are targeted by de novo DNA methyl transferees in a sequence-specific manner, but this has not been tested. Overall, this review aims at different genes involved in colorectal cancer.

Introduction

Colorectal cancer (CRC) is the most common malignancy in the digestive system and has high incidence and mortality[1]. Metastasis is the main cause of CRC-related mortality. The mechanisms governing tumor growth and metastasis have been extensively investigated but remain poorly understood4. It features amongst the three most widely spread malignancies worldwide, characterized by diverse clinical phenotypes and responses to current treatments. Indeed, one of the most prominent CRC features is its considerable interpatient heterogeneity. The 5-year survival rate for CRC is over 90% for stage I disease, but it is below 10% when CRC develops into advanced stage IV disease with metastasis5. The American Cancer Society has lowered the recommended age for regular screening from 50 to 45 in people with average risks of CRC, and increases in the screening rate via colonoscopy partly account for the global rise in the incidence of CRC6 [2] . When CRC progresses to advanced stages, especially with fatal distant metastases, targeted therapies are an essential component of the comprehensive treatment regimen Recent years have seen numerous efforts to classify genetically and phenotypically diverse CRC tumors into distinct molecular subtypes based on gene expression profiling. These studies highlight the challenges in identifying a consensus molecular classification system and the urgent need to re-assess inter patient variability through the prism of a shared regulatory architecture. Epigenetic deregulation has emerged as a paradigm of cancer biology that underlies the hallmarks of cancer cells2 Within the intestinal lamina propria, stromal cells include fibroblasts, α-smooth muscle actin (αSMA)- positive my fibroblasts, endothelial cells, and pericytes. These stromal cells organize the tissue architecture and have recently been revealed to play crucial roles in regulating immune responses, tissue repair, and tumour development [3]. Recent studies have focused on fibroblasts that can support tumour growth, termed cancer-associated fibroblasts (CAFs). In a recent study, single cell RNA sequencing (scRNA-seq) was performed to analyse colon biopsies from healthy individuals and ulcerative colitis (UC) patients. The results revealed that UC patients' colon samples include a unique subset of fibroblasts, termed inflammation associated fibroblasts (IAFs), with high expression of Interleukin 11 (IL11), IL24, IL13RA2, and TNFSFR11B. 1 D NA methylation is an epigenetic mark associated with gene repression. It is normally pervasive in mammalian genomes but absent from many regulatory elements, particularly CpG islands (CGIs). In tumours, CGIs often become aberrantly methylated. In some cases hyper methylated CGIs correspond to the promoters of tumour suppressor genes such as MLH1, CDKN2A (p16/ARF) and BRCA13. The human BCL9 gene, a homolog of the Drosophila segment polarity gene Legless was first identified in a (1; 14) (q21; q32) translocation from a patient with precursor Bcell acute lymphoblastic leukemia (B-ALL). BCL9/Legless is a transcriptional co-activator of the canonical Want pathway and bind to β-catenin through a highly conserved HD2 domain8[4].

Results

IL-11+ cells: To characterize IL-11-producing (IL-11+) cells in vivo, a transgenic mice was generated in which Egfp expression was under the control of the Il11 gene promoter, using a bacterial artificial chromosome (BAC) vector An Egfp cDNA and a polyA signal were inserted in-frame in the second exon of the Il11 gene. As expected, Il11 mRNA expression was correlated with Egfp mRNA expression in various tissues. Notably, Il11 mRNA expression was highest in the testis and was very low in other mouse tissues under normal conditions Next, isolated and characterized IL-11+ cells from tumors of Il11-Egfp reporter mice. We observed that the percentage of cells that were EGFP (IL-11)+ was increased in tumor tissues compared with nontumor

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colon tissues from AOM/DSStreated Il11-Egfp reporter mice. The majority of IL- 11+ cells expressed mesenchyme stromal cell markers, such as Thy1.2, podoplanin, CD29, and Sca-1, but not CD31 or Lyve-1, whereas only very small percentages of IL-11+ cells expressed EpCAM. Conversely, only 5% of podoplanin+ cells (mostly fibroblasts) expressed IL-11 [5]. Immunohistochemistry (IHC) revealed that IL-11+ cells appeared in the stroma surrounding tumor cells1. patients' samples were collected and used to generate organoids, performed histo pathological and molecular characterization of organoids validating them as surrogates of the primary tumors from which they derive, and established their genome-wide epigenetic landscape. In the first step, we obtained a pool of PDOs recapitulating the molecular heterogeneity of human CRC. For this, we performed RNAsequencing (RNA-seq) on the primary tumors (from surgical resection) and screened them for markers of microsatellite instability (MSI) and three recently published gene expression classifiers, contextually generating PDOs from the same donors. Upon primary tumor analysis, we selected a collection of 10 PDO lines representing a balanced library that recapitulates the molecular diversity of the cancer-cell intrinsic features of human primary CRCs. Next, we validated that our PDOs preserve the histo pathological and molecular features of primary tumors. We first tested whether PDOs retained the typical morphological characteristics and the deregulated architecture of crypt/villus-like structures of human CRC. By using 3D immunofluorescence whole-mount analysis, PDOs displayed disorganized epithelial polarity. EpCAM and F-actin staining respectively, random distribution of cell proliferation, displaced localization of enterocytes and presence of cytokeratin 20 positive cells, recapitulating the common dysplastic features of human CRC2.

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