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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 remain 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 (IL-11$^+$) 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 methyltransferases in a sequence-specific manner, but this has not been tested. Overall, this review aims at different genes involved in colorectal cancer.

Keywords: Colorectal cancer; EO-CRC; Cytokines; Colorectal tumours

Introduction

Colorectal Cancer (CRC) is the most common malignancy in the digestive system and has high incidence and mortality. Metastasis is the main cause of CRC-related mortality. The mechanisms governing tumor growth and metastasis have been extensively investigated but remain poorly understood. 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 metastasis. 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 CRC [1]. 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 interpatient 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 cells within the intestinal lamina propria, stromal cells include fibroblasts, α-smooth muscle actin (αSMA)-positive myofibroblasts, 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 tumor development [2].

Recent studies have focused on fibroblasts that can support tumor growth, termed Cancer-Associated Fibroblasts (CAFs). In a recent study, single cell RNA sequencing (scRNA-seq) was performed to analyze 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 hypermethylated CGIs correspond to the promoters of tumour suppressor genes such as MLH1, CDKN2A (p16/ARF) and BRCA1. 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 Wnt pathway and bind to β-catenin through a highly conserved HD2 domain.

Results

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 colon tissues from AOM/DSS- treated Il11-Egfp reporter mice. The majority of IL- 11^{+} cells expressed mesenchymal 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. Immunohistochemistry (IHC) revealed that IL-11^{+} cells appeared in the stroma surrounding tumor cells1. patients' samples were collected and used to generate organoids, performed histopathological 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 RNA- sequencing (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. Next, we validated that our PDOs preserve the histopathological 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 random distribution of cell proliferation, displaced localization of enterocytes and presence of cytokeratin 20 positive cells, recapitulating the common dysplastic features of human CRC [3].

Cell populations carrying CGI integrations were then expanded for 4 weeks to ensure free plasmid was no longer present in the population before we determined DNA methylation levels at the integrated copies and native loci using specific bisulfite PCR primers. Each ectopically integrated copy assayed will derive from a separate integration site in the population of transfected cells thus sampling a diverse array of different genomic locations. The BUB1 and MLH1 CGIs both remained unmethylated when integrated into ectopic locations using piggyback. The vast majority of integrated copies of the aberrantly methylated CGIs tested also did not become de novo methylated. Rare cases of methylation observed at integrated copies were low level and heterogeneous but confirmed that HCT116 cells are capable of de novo methylation as previously reported. The highest levels of methylation observed were at ectopic copies of the CDH13 CGI but these were still much lower than those seen at the native locus.

To determine the potential role of AGO2 in CRC, we measured the expression of AGO2 in 213 paired cancer tissues and corresponding normal tissues by multiplex fluorescent IHC and a scoring system based on InForm software . We found that AGO2 was significantly expressed at lower levels in cancer tissues. And the expression of AGO2 was significantly higher in cancer tissues than in stromal tissues. Consistently, we found that the AGO2 protein was downregulated in primary colon tumor tissues in the CPTAC data. It has been widely accepted that Epithelial-Mesenchymal Transition (EMT) is associated with the loss of E-cadherin and the upregulation of vimentin.

The median age was 36 years (range, 22-41), and 25 (53%) patients were male. Of 47 tumors, 38 (81%) were at stage 3 or 4 at diagnosis, and 36 (77%) were located in the left colon. The cases were grouped into mutant POLE, MSI, and MSS subtypes. Mutant POLE and MSI tumors were more prevalent in male patients and in the left colon. Approximately two-thirds (64%) of the patients had a family history of cancer, and 12 (26%) had a family history of colon cancer. After excluding two samples diagnosed with familial adenomatous polyposis, we analyzed recurrently mutated genes in 35 non-hypermutated, noncancer syndrome samples. Genes mutated in LO-CRC were also commonly mutated in EO-CRC, albeit with slight differences in the order of mutation frequency. TP53 was the most commonly mutated gene, and the mutation frequency was higher than that previously reported. We additionally summarized 833 panel-seq data. (AMC_panel) composed of 99 EO-CRC and 734 LO-CRC samples with TCGA and MSK data. The patient characteristics of all cohorts. EO-CRC showed a higher frequency of TP53 mutation (80% vs 72%, Fisher's exact P=0.03) and lower frequencies of APC (65% vs 78%, P<0.001) and KRAS (37% vs 45%, P=0.01) mutation than LO-CRC [4].

Gene Expression Profiling Interactive Analysis (GEPIA) analysis found that LMNB2 is differentially expressed in CRC. We tested the expression of LMNB2 in 12 pairs of tumor tissues and adjacent tissues, and found that LMNB2 expression was significantly increased in the CRC tissues. Western blotting analysis showed that LMNB2 was pervasively highly expressed in CRC cell lines but expressed at relatively low levels in normal colonic epithelial cells (FHC). We analyzed 226 tumor and adjacent tissues, and immunohistochemical staining showed that LMNB2 was mainly located in the nuclear membrane of the nucleus. Pairing the tumor tissue with the adjacent tissue and performing a paired Wilcoxon's test revealed that the LMNB2 protein expression in the cancer tissue was significantly higher than that in the adjacent tissue. The data showed that CRC patients with high LMNB2 protein expression had worse OS and disease-free cumulative survival.

Discussion

In this study, we generated Il11-Egfp reporter mice to characterize IL-11^{+} cells in different murine tumor and colitis models. We found that the IL-11^{+} cells in tumor tissues were mostly fibroblasts and a few epithelial cells and that deletion of Il11ra or Il11 attenuated CAC development in mice. BM transfer experiments revealed that IL-11^{+} fibroblasts critically contributed to tumor progression and that IL-11+ fibroblasts were not derived from BM. IL-11 efficiently activated IL-11^{+} colonic fibroblasts and colon tumor organoids. Transcriptome analysis showed that IL-11^{+} fibroblasts expressed genes associated with tissue repair and cell proliferation. Thus, IL-11^{+} fibroblasts produce several growth factors that induce the proliferation of nearby tumor cells. The exploitation of primary tissue-derived tumor organoids, allowed us to dissect cancer cell-intrinsic epigenetic alterations devoid of the influence of stromal cells, and provided sufficient material to perform a systematic de novo discovery of biologically informative chromatin states. By combining more than 66 chromatin maps for multiple histone marks we identified 8 different epigenetic states, revealing the genome-wide location of promoter and enhancer regions, as well as elongating and repressed genomic regions. This data generates an extensive functional annotation of the

human genome in CRC allowing the interrogation of diverse modes of epigenetic regulation. Our observation that the highest levels of de novo methylation at CGIs in cancer cells are targeted towards those associated with H3K36me3 parallel observations made in diverse systems. Both DNMT3A and DNMT3B possess a PWWP domain that binds H3K36me3. In mouse embryonic stem cells Dnmt3b is primarily localised to H3K36me3 and Dnmt3b knockout leads to preferential loss of DNA methylation from H3K36me3 marked regions. H3K36me3 is deposited by SETD2 through its association with RNA polymerase II.

Transcription-induced deposition of H3K36me3 leads to Dnmt3b-dependent methylation of CGIs in mouse ES cells. Implications of MEF2A in human cancer were discovered in prostate cancer, and MEF2A was shown to participate in stress-induced progression of prostate cancer as a p38 substrate [5]. MEF2A is phosphorylated by p38MAPK in gastric cancer and promotes tumor proliferation and metastasis. In breast cancer, MEF2A is activated by TGF-β and mediates TGF-β-induced breast cancer metastasis by upregulating MMP10. By integrating mutation, chromosomal copy number, and clinical information, we divided CRC by the carcinogenesis step into three subgroups: a hypermutated group, which includes EO-CRC with predisposing germline variants; a WGD group with early TP53 mutation, genome doubling, and focal oncogene amplification leading to malignancy; and a GS group, which follows conventional colorectal carcinogenesis, exhibiting point mutations in APC, KRAS, TP53, and deletion of tumorsuppressor genes. The occurrence and development of tumors is a multifactor and multistep complex process that includes oncogene activation and tumor suppressor gene inactivation. Therefore, exploring the exact molecular mechanism of CRC progression is important.

References

1. Nishina T, Deguchi Y, Oshima D, Takeda W, Ohtsuka M, et al. (2021) Interleukin-11-expressing fibroblasts have a unique gene signature correlated with poor prognosis of colorectal cancer. Nat Commu 12: 2281.
2. Chiara Gd, Gervasoni F, Fakiola M, Godano C, Azzolin L, et al. (2021) Epigenomic landscape of human colorectal cancer unveils an aberrant core of pan-cancer enhancers orchestrated by YAP/TAZ. Nat Commu 12: 2340.
3. Masalmeh RHA, Taglini F, Rubio-Raman C, Musialik KI, Higham J, et al. (2021) De novo DNA methyltransferase activity in colorectal cancer is directed towards H3K36me3 marked CpG islands. Nat Commu 12: 694.
4. Xiao Q, Gan Y, Li Y, Fan L, Liu J, et al. (2021) MEF2A transcriptionally upregulates the expression of ZEB2 and CTNNB1 in colorectal cancer to promote tumor progression. Oncogene 40: 3364-3377.
5. Dong CH, Jiang T, Yin H, Song H, Zhang Y, et al. (2021) LMNB2 promotes the progression of colorectal cancer by silencing p21 expression. Cell Death Dis 12: 331.