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REVIEW

Molecular Complexity of Colorectal Cancer: Pathways, Biomarkers, and Therapeutic Strategies

Zhengdong Yang, Xinyang Wang, Huiying Zhou, Minghan Jiang, Jinghui Wang, Bowen Sui

The First Department of Oncology, Heilongjiang University of Chinese Medicine, Heilongjiang, 150040, People's Republic of China

Correspondence: Bowen Sui, The First Department of Oncology, Heilongjiang University of Chinese Medicine, Heilongjiang, 150001, People's Republic of China, Email suibowen79@sina.com

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Abstract: Colorectal cancer (CRC) is a diverse disease entity and a leading cause of cancer-related mortality worldwide. CRC results from the accumulation of multiple genetic and epigenetic alterations. This heterogeneity of CRC underscores the significance of understanding its molecular landscape, as variations in tumor genetics can greatly influence both patient prognosis and therapeutic response. The molecular complexity of CRC is defined by three major carcinogenesis pathways: chromosomal instability (CIN), microsatellite instability (MSI), and the CpG island methylator phenotype (CIMP). These pathways contribute to the onset and progression of CRC through mutations, epigenetic modifications, and dysregulated cellular signalling networks. The heterogeneous nature of CRC continues to pose challenges in identifying universally effective treatments, highlighting the need for personalized approaches. Hence, the present review aims at unravelling the molecular complexity of CRC that is essential for improving diagnosis, prognostication, and treatment. We detail on the current understanding of the molecular framework of CRC, central signalling pathways of CRC associated with its initiation to a malignant phenotype, further invasion, progression, metastases, and response to therapy. Continued research into CRC's pathways and biomarkers will pave the way for the development of more precise and effective therapeutic strategies, ultimately improving patient outcomes.

Keywords: colorectal cancer, molecular mechanisms, pathways, chromosomal instability, adenomatous polyposis coli, biomarkers

Introduction

Colorectal cancer (CRC) refers to the uncontrolled growth of cells formed at the lower end of the digestive tract. Cancerous growth in the colon and rectum is known as colorectal cancer (CRC). Worldwide, CRC is the third leading cause of cancer-related mortality worldwide. In 2020, an estimated 1,880,725 individuals were diagnosed with CRC. It is the third most commonly diagnosed cancer and the second leading cause of cancer-related deaths globally, following lung cancer.[1] Furthermore, in the US, CRC has been identified as the second most common cause of cancer-related deaths due to cancer when the numbers of men and women are both considered with an estimated 153,020 new cases of CRC and were expected to be diagnosed, and around 52,550 deaths were projected.[2]

CRC manifests itself in the beginning as noncancerous polyps. It develops in the inner mucosal layers of the colon and rectum. Although polyps are commonly detected in individuals 50 years of age or older during colonoscopy, fewer than 10% of these polyps are estimated to progress towards developing cancer.[3] Adenomatous (ie adenoma) or serrated polyps are common cancer precursors. Accumulating evidence suggests that CRCs are a group of molecularly heterogeneous diseases with many genetic and epigenetic alterations that participate in the development of the disease.[4,5] This highly heterogeneous nature of the disease tends to significantly influence tumor initiation, its progression, resistance, response to therapy and overall clinical outcome. Despite significant progress, critical gaps remain in understanding how this molecular complexity can be fully harnessed to improve patient outcomes. A significant challenge lies in tumor heterogeneity, both between patients (inter-tumoral) and within a single tumor (intra-tumoral), which complicates the discovery of universal biomarkers and treatment approaches. Although certain biomarkers, such as microsatellite instability (MSI) and mutations in genes like KRAS, BRAF, and TP53, have clinical significance, numerous others remain unexplored. Furthermore, resistance to existing therapies, especially in advanced and metastatic CRC, underscores the need for a better understanding of how molecular changes contribute to treatment failure. The development of

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novel biomarkers for early detection, prognosis, and therapy response is critical, as is the identification of new therapeutic strategies that can address the inherent heterogeneity and treatment resistance in CRC.

Here, we present a simplified insight into the current knowledge and recent developments pertaining to the molecular network and central signalling pathways of CRC associated with its initiation to a malignant phenotype, further invasion, progression, metastases, and response to therapy. This understanding is essential for the discovery and testing of future treatment therapies targeting the respective molecular pathways. Three major molecular pathways leading to CRC are discussed in detail: a) Chromosomal Instability (CIN) pathway, b) CpG Island Methylator Phenotype (CIMP) pathway, and c) Microsatellite Instability (MSI) pathway.

CIN Pathway and CRC

The frequency of the baseline mutation rates under normal conditions is too low and insufficient for cancer development. Thus, a chromosomal instability is observed in as high as 65–70% cases of colorectal cancers.[5,6] CIN refers to a type of genomic instability with accelerated rates of unstable chromosomes, wherein either the whole chromosome or a portion of the chromosome is duplicated or deleted.[7] Numerical CIN, also known as aneuploidy, is a common form seen. Under normal conditions, errors in chromosomal segregation leading to changes in the number of chromosomes occur in less than 1% of cell divisions but cells with CIN exhibit enhanced error rate of ~20%.[8] Structural CIN is different, and portions of whole chromosomes may be duplicated or deleted, or there may be a rearrangement of parts of the chromosomes.[9] Multiple causes lead to a higher normal rate of abnormalities in the whole or part of the chromosome. Not diving into the detail, briefly, the major causes include a) breakdown in the cell's repair mechanism may lead to chromosome rearrangements that result in the loss, amplification, and/or exchange of chromosome segments. For example, ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR) protein kinases are DNA repair proteins, whose inactivation mutations have been implicated in the development of human cancer.[10] With inactivating mutations in TP53 that result in the loss of its function, uncontrolled entry into the cell cycle occurs, and this functional loss of TP53 has been directly implicated in human CRC.[11,12] Telomere dysfunction is a major cause of CIN. Telomeres are specific DNA-protein structures present at both ends of each chromosome and play a crucial role in protecting against nucleolytic degradation, unnecessary recombination, inter-chromosomal fusion, and breakage during segregation. During every round of cell division, a portion of telomeric DNA is lost.[13] Once a significant number of divisions occurs (25–50), telomeres can be completely lost with the induction of p53 expression, which permanently arrests the cell or induces apoptosis. The shortening of telomeres and p53 expression form a protective barrier against uncontrolled replication and tumour development. However, inactivating mutations leading to nonfunctional p53 cause shortening of telomeres with eroded portions prone to chromosomal rearrangements through recombination and repeated breakage-fusion-bridge (B/F/B) cycles.[14] Continuation of B/F/B cycles for multiple cell divisions may lead to undesirable changes in genome organisation. Studies have indicated that shorter telomeres were observed in 77% to 90% of colon cancer samples, compared to adjacent normal tissues.[15,16] Defects in chromosome segregation during the mitotic cycle are another cause of CIN. Spindle assembly checkpoint (SAC) and mitotic checkpoint controls are key regulators of chromosome segregation during mitosis and meiosis. It delays the start of the anaphase until all pairs of duplicated chromatids are correctly positioned on the metaphase plate.[17] Checkpoint signalling defects cause chromosome mis-segregation and subsequent aneuploidy, in which daughter cells receive abnormally large numbers of chromosomes.[18] The CIN pathway has been associated with several genetic events. Whether CIN enables the creation of an appropriate environment for the accumulation of these mutations or whether these mutations lead to CIN remains unresolved. The major genes involved in this process are discussed below.

APC (Adenomatous Polyposis Coli) Gene Mutation

The most important of all is the APC gene which is classified as a tumor suppressor gene. This gene is located on chromosome 5q21-q22, which consists of 8535 nucleotides with 21 exons. *APC* encodes a 310 kDa protein, *Adenomatous polyposis coli* (APC). This protein has multiple domains that primarily consist of an oligomerization domain, an armadillo repeat domain, 15- or 20-residue repeat domain, a SAMP repeat domain, a basic domain, and a C-terminal domains.[19,20] Through its multiple binding partners, APC is involved in cellular processes, such as cell

migration, adhesion, differentiation, and chromosomal segregation. APC functions as a critical negative regulator of the canonical WNT/β-catenin pathway. It acts as a scaffold structure for the destruction complex that promotes phosphorylation and subsequent ubiquitin-dependent degradation of CTNNB1(Catenin beta-1), a key WNT pathway activator.[21,22] APC enhances the effectiveness of this destruction machinery by encouraging axin multimerization and stabilising the axin complex.[23] If the APC is rendered inactive by a mutation, an excessive build-up of CTNNB1 in the cytoplasm results, which then translocates to the nucleus. This controls transcriptional changes that promote *MYC* expression and activation of other oncogenes. Interruption of the WNT pathway dysregulates colonic epithelial cell proliferation and proper differentiation, leading to progression from low-grade to high-grade adenomas.[5,24] This is because other tumour suppressor genes are rendered inactive. Additionally, functional APC loss could affect the regulation of mitotic processes, which adds to the structural or numerical CIN. Approximately, 60% of colon tumours and 82% of rectal cancers have APC mutations.[25]

K-RAS Gene Mutation

KRAS (12p12) is another important gene in the CIN pathway; however, it is also associated with the CIMP pathway. The Kirsten rat sarcoma virus oncogene homolog (Ki-ras2) gene is an oncogene that produces the 21 kDa GTPase transductor protein KRAS. KRAS controls cell division because of its ability to relay external signals to the cell nucleus.[26] Most human cells express KRAS, a membrane-bound GTP/GDP-binding protein with an intrinsic GTPase activity. Under normal conditions, binding of growth factors to their respective cell surface receptors activates guanine exchange factors (GEF), such as SOS (son of sevenless), which are attached by the adaptor protein GRB2 (growth-factor-receptor bound protein 2). Bound GDP is released from RAS and exchanged for GTP in response to SOS stimulation, creating an active RAS-GTP conformation. Multiple effector pathways, including the Raf-MEK-ERK pathway, PI3K, RALGDS, RALGDS-like gene (RLG), and RGL2, are regulated by the activated RAS. These downstream effectors have a wide range of effects, such as prevention of apoptosis, stimulation of cell growth, cell transformation, angiogenesis, migration, and differentiation.[26,27] GTPase-activating proteins (GAP) can bind to RAS-GTP and accelerate its conversion to guanosine diphosphate (RAS-GDP), causing signal termination.[28] KRAS mutations decrease the intrinsic GTPase activity of the protein, causing a build-up of active GTP-bound KRAS proteins. Codons 12 and 13 of exon 2 and, to a lesser extent, codon 61 of exon 3 are the most common single nucleotide point mutations.[29] Mutant KRAS stops responding to GAPs and quickly converts GDP to GTP, thereby locking it in its active state.[26] This results in the constitutive activation of downstream effector activities, thus promoting uncontrolled cell growth and transformation, cancer spread, and enhanced resistance to chemotherapy in many cancer types, including CRC.[30,31] KRAS mutations have been linked to poor prognosis for CRC and lung and liver metastases according to a number of studies. Approximately 30–40% of CRCs harbour *KRAS* mutations.[32,33] KRAS mutations in colon cancer have been associated with poor survival, increased tumour aggressiveness, and resistance to select treatment strategies.[31,34] Table 1 highlights

Table 1 Major Molecules Targeting the KRAS Pathway, Developed for Therapeutic Testing Against CRC Development Along with Category, Their Mode of Action and Current Clinical Status

Category	Candidate Molecule	Mode of Action	Current Status	Related Reference
Direct KRAS Inhibitors	AMG 510 (Sotorasib)	A specific, irreversible inhibitor of KRAS G12C that traps the KRAS in its inactive GDP-bound state	Approved in NSCLC, ongoing clinical trials in CRC	[35]
Direct KRAS Inhibitors	MRTX849 (Adagrasib)	Small-molecule specific inhibitor of mutant KRAS G12C protein	Phase II/III clinical trials	[36]
Polo-like kinase 1 (PLK1) inhibitors	Onvansertib	Selective and oral inhibitor of PLK1, a key regulator of cell division and mitosis.	Phase I/II clinical trials	[37]

(*Continued*)

Table 1 (Continued).

Category	Candidate Molecule	Mode of Action	Current Status	Related Reference
Antimicrobial peptides (AMPs)	KR12	Recognizes and Alkylates adenine residues on the template strand at codon 12 (GTT and GAT), exon 2 of mutated KRAS, producing strand cleavage and decreasing the proliferation rate of the CRC cell with G12D/G12 V mutation.	Tested only in preclinical studies	[38]
KRAS-PDEδ interaction inhibitor.	Deltarasin	Inhibition of Prenyl-binding protein PDEδ (a protein essential for maintaining the spatial organization of RAS for effective signalling) blocking the oncogenic RAS signalling	Phase I/II clinical trials	[39]
Immuno-oncolytic virus therapy	Pelareorep	Oncolytic reoviruses that selectively infects the *KRAS* mutated CRC cells inducing lysis and promoting autophagy	Currently advancing towards Phase III clinical trials	[40,41]
Nucleic acid antisense oligonucleotide	AZD4785	Genetically engineered molecule functions as an antisense oligonucleotide complementary to mRNA sequences of KRAS causing exhaustion of intracellular KRAS mRNA and protein.	Studied in Phase I clinical trials	[42]
Small molecule kinase inhibitors	AZD6244 (Selumetinib)	Selective oral mitogen-activated protein kinase (MAPKK, or MEK) pathway inhibitor. The drug interacts with MEK1/2 by turning MEK1/2 into their inactive conformational states.	Studied in Phase I and II settings	[43]

the major biomolecules based on the KRAS pathway that have been developed for therapeutic purposes, with their mechanisms of action and current clinical status.

Impairment of TP53

One of the key genes responsible for the transformation of colorectal cancer (CRC), and its aggressive and metastatic characteristics, is TP53. As one of the most crucial components of the body's anticancer defense system, this gene is a critical tumour suppressor. The gene product, which is a 393 amino acid transcription factor located on the short arm of chromosome 17, serves as a tumour suppressor and a key coordinator of cellular responses to oxidative stress, DNA damage, and aberrant proliferative signals.[44,45] The transcription of hundreds of genes involved in DNA metabolism, apoptosis, cell cycle regulation, senescence, angiogenesis, immunological response, cell differentiation, motility, and migration is regulated by the master regulator p53.[46,47] Under normal conditions, once activated, MDM2 (murine/human double minute 2), a negative regulator, is upregulated. MDM2 acts as an E3 ubiquitin ligase and attaches to the p53 transactivation domain, causing ubiquitination and p53's destruction.[48,49] This creates a negative feedback loop that maintains low p53 levels in the normal cells.

Documented data suggest that 4%–26% of adenomas, 50% of adenomas with invasive foci, and 50%–75% of CRCs have been associated with functional loss of p53. Thirty-four percent of proximal colon tumours and 45% of distal colorectal tumours in CRC have been shown to have p53 mutations. These statistics highlight the key role of these molecules in the transformation of adenomas to carcinomas.[50,51] The majority of TP53 mutations are missense changes that affect exons 5 to 8 (the DNA-binding domain), primarily at hotspot codons, such as 175, 245, 248, 273, and 282, which result in the synthesis of an inactive protein with an abnormally extended half-life.[51,52] p53 mutations are associated with lymphatic invasion in proximal colon cancer and are strongly correlated with both lymphatic and vascular invasion in distal colon cancer. Additionally, individuals with CRC who have mutant p53 show higher chemoresistance and worse prognosis than those with wild-type p53.[53] These observations suggest that the reactivation and restoration of p53 function have a great potential as novel therapeutic strategies for CRC treatment. Table 2 briefly details the various p53-based treatment options explored for the treatment of CRC. Most of the candidate molecules have shown promising results as tested in cell lines or in animal models, and clinical data on these are the need of the hour so as to translate these p53-based therapies for clinical use for CRC patients.

Other Genes

In addition to the above genes, later events in the pathogenesis of CRC include deletions on chromosome 18q, with a high proportion observed in cases of colorectal cancer.[63] One gene, *Cables*, a novel regulatory protein mapped to

Table 2 Molecules Based on p53-Based Treatment Approaches Being Explored for CRC, Along with Their Mode of Action and Clinical Progress Status

Candidate Molecule	Mechanism of Action	Therapeutic Potential in CRC	Ongoing Status	Related Reference
PRIMA-1 (p53 Reactivation and Induction of Massive Apoptosis)	Restores wild-type function of mutant p53, inducing apoptosis.	Induces apoptosis in CRC cells harbouring mutant p53, sensitizes to other treatments.	Preclinical and early clinical trials	[54]
MI-219	MDM2-p53 inhibitor	Induces apoptosis in HCT-116 colon cancer	Promise in preclinical studies, not yet advanced further	[55]
Nutlin-3 (R1772)	Occupy the binding pocket of MDM2, thus disrupting MDM2-p53 interaction	Reactivates p53-dependent apoptosis in CRC cells, enhancing chemotherapy efficacy	Preclinical and early clinical trials	[56]
RITA	Directly binds to p53 and induces a conformational change in p53, causing interfered p53-MDM2 interaction causing p53 accumulation and cellular apoptosis	Induces apoptosis in CRC cells, both p53 wild-type and mutant.	Preclinical trials	[57]
Tenovins	Inhibit SIRT1/2 deacetylases, stabilizing p53 and enhancing its tumor-suppressing activity.	Increases p53-mediated apoptosis and enhances response to chemotherapy in CRC.	Preclinical trials	[58]
Machinic acid (MA)	Natural triterpene from *Olea europaea*, that works by inducing the expression of JNK (c-Jun NH2-terminal kinase) and p53 resulting in cell cycle arrest and apoptosis	Shows anticancer activity by reactivating p53 in CRC cells.	Preclinical trials	[59]
Epicatechin gallate	Natural polyphenol found in green tea, causing stimulated expression of p53, p21, and MAPKs (mitogen-activated protein kinases) in CRC cell lines	Inhibits CRC cell growth via p53 activation, enhances antioxidant defense.	Preclinical trials	[60]
Lipoic acid (α-LA)	α-LA inhibits proliferation and induces apoptosis in colon cancer cells by preventing p53 degradation	Enhances p53-mediated apoptosis in CRC, reduces cancer cell viability.	Preclinical trials	[61,62]

chromosome 18q11.2–12.1, is lost at a high frequency in colon cancer. This protein connects to, or acts as a cable for, other crucial proteins involved in carcinogenesis and cell proliferation. Cables interact with serine/threonine protein kinase cyclin-dependent kinase (cdk) and increase tyrosine phosphorylation, which reduces kinase activity and decreases cell growth. Cables interact with the p53 tumour suppressor gene to increase p53-induced apoptosis.[64] Loss of *Cables1* expression, evaluated by immunohistochemistry, has been found to be decreased or absent in 65% of primary CRCs,[65] correlating with the loss of heterozygosity at 18q. Kirley et al[63] studied the susceptibility of *Cables-/-* mice to colon tumour development. This Twenty weeks of subcutaneous 1.2-dimethylhydrazine (DMH) injections were administered to *Cables-/-* mice and their *Cables+/+* littermates. Compared with their *Cables+/+* littermates, *Cables-/-* mice had considerably lower median survival times following DMH injections. The number of colorectal tumours that developed in *Cables-/-* mice was 46 tumours versus 21 tumours. In another study by Arnason et al,[65] the role of *Cables*1employing

an in vivo mouse model of intestinal adenocarcinoma. *ApcMin/+* mice were crossed with mice harbouring the targeted inactivation of *Cables1* (*Cables1−/−*). Results showed that the mean number of small intestinal tumors per mouse was 3.1 ± 0.6 in *Cables1+/+ ApcMin/+* mice, and in *Cables1−/−ApcMin/+* mice, this values was 32.4 ± 3.5. In addition, tumours from *Cables1−/−ApcMin/+* mice demonstrated an increased nuclear expression of β-catenin, showing that loss of *Cables1* enhanced tumour progression in the *ApcMin/+* mouse model and activated the Wnt/β-catenin signalling pathway.

Additional genes reported in 18q were deleted in Colorectal Carcinoma (*DCC), SMAD4*, and *SMAD2*.[66,67] However, the product of *DCC* is a cell surface receptor for the neuronal protein netrin-1, and *DCC* mutations have rarely been detected in colorectal tumours (6%).[7,68] Similarly, SMAD4 and SMAD2 mutations have been found in less than 10–20% cases of colon cancers,[69,70] and thus more data need to be examined to understand the role of these genes, if any, in CRCs.

Overexpression of COX-2 in CRC

In addition, evidence suggests that Cyclooxygenase-2 (COX-2) plays a significant role in the development of CRC.[71,72] There are three isoforms of COXs: crucial regulators of angiogenesis, inflammation, and carcinogenesis (COX 1–3). COX-2 is an inducible isoform in normal tissues, such as the colon, kidney, reproductive organs, and stomach organs.[73] High expression with constant upregulation of COX-2 is observed in various premalignant and malignant lesions of epithelial origin as well as in different regions of the gastrointestinal tract.[71,74,75] Tumours with high levels of COX-2 are relatively more aggressive,[71] and patients with these tumours have significantly reduced survival rates.[76] In a study by Oshima et al,[77] which was the first to directly demonstrate the role of COX-2 overexpression in the early stages of polyp development, the Apcdelta716 mouse's intestinal and colonic polyps decreased in number and size in a dose-dependent manner after treatment with a specific COX-2 inhibitor, rofecoxib.

Arachidonic acid (AA) serves as a substrate for COX-2, which mediates the biosynthesis and release of prostaglandins. PGE2 is the primary prostaglandin, contributing to colorectal progression. PGE2 operates on receptors (EP1, EP2, EP3, and EP4) to induce a signal cascade with changes in intracellular calcium and cAMP, and a prolonged PGE2 increase initiates pathological events, cancer genesis, and spread.[78] Recent investigations have shown that PGE2 may enhance the progression of colorectal cancer[79,80] and that EP4 is a therapeutic target for cancer therapy.[81,82] In addition, COX-2 is involved in regulating angiogenesis, and overexpression of COX-2 increases the production of pro-angiogenic factors that contribute to tumour vascularity and growth.[83] Negi et al[72] studied mRNA expression levels of COX-2 in thirty CRC patients. They found that COX-2 overexpression in patients with colorectal cancer was related to clinicopathological factors and that COX-2 mRNA expression may serve as a biomarker for the diagnosis of CRC.

MSI Pathway and CRC

Microsatellites, also referred to as simple sequence repeats (SSRs), are repeat DNA sequences that range in length from one to six base pairs and are found next to one another in the genome. Microsatellite instability (MSI) is a genetic hypermutability condition caused by a faulty DNA mismatch repair (MMR).[84,85] More specifically, mutations inserted into microsatellite regions are not corrected when there are errors in mismatch repair (MMR) genes (MLH1, PMS2, MSH2, MSH6), leading to MSI.[86] It has been observed that 10–15% of CRC are associated with MSI and are MMR deficient (dMMR).[87] Under normal conditions, the cell's MMR system effectively starts to function to take care of any introduced microsatellite instability through a cascade of events involving the interaction of MMR proteins as heterodimers, such as MSH2–MSH6 (MutSα), MLH1-PMS2 (MutLα), and SH2–MSH3 (MutSβ), and further excision with the help of proteins, that is, exonuclease 1 and proliferating-cell-nuclear antigen, followed by re-synthesis and re-ligation of the DNA strand.[86,88] MSI tumours carry mutations in the coding regions of several genes including BRAFV600E, TGFβRII, BAX, and IGFIIR. Two molecular pathways lead to the development of CRCs with MSI. The first are germline mutations in MMR genes, which lead to hereditary nonpolyposis colorectal cancer (HNPCC), that is Lynch syndrome, an autosomal dominant disorder. The second most common mechanism is epigenetic inactivation of *MLH1* due to somatic hypermethylation of CpG islands surrounding the promoter region of *MLH1* and other genes. Approximately 15% of all colorectal malignancies have MSI; 3% of them are linked to Lynch syndrome, while the remaining 12% are brought on by spontaneously acquired hypermethylation.[89,90] However, many CRCs have an intact

MMR system but frameshift mutations in a few microsatellites.[91] CRCs with MSI have distinctive pathological features, including a tendency to arise in the proximal colon, poorly differentiated tissue, high mucinogens, and tumour-infiltrating lymphocytes.[92,93] CRC with MSI does not respond to 5-fluorouracil (5-FU) treatment; thus, MSI is a negative predictive marker of the response to 5-FU. HCT116 colon cancer cells with a homozygous mutation in hMLH1 on human chromosome 3, which display microsatellite instability and resistance to 5-FU, were used in a study by Koi et al.[94] However, with the transfer of chromosome 3, which restored the copy number of the functional MLH1 gene, the sensitivity to 5-FU was restored (39) was regained back. Similar observations were noted when studying the response to 5-FU in human colon cancers (hCC) with MSI orthotopically xenografted into nude mice.[95] In a systematic study by Popat and team,[90] it was found that the survival rate of CRC patients with MSI was higher than that of CRC patients with microsatellite stable (MSS) tumours, and colorectal tumours with MSI have a slightly better prognosis than colorectal tumours without MSI.[96] However, more conclusive data from larger prospective trials are required to establish the clinical significance of MSI in CRC treatment.

The CpG Island Methylator Phenotype (CIMP) Pathway

The second most frequent pathway in sporadic CRCs is CIMP. Fifteen% of sporadic cases are caused by the CIMP pathway.[97,98] The CIMP pathway is the basis of epigenetic instability. Epigenetic changes refer to changes in gene expression without corresponding changes in DNA sequence. Studies have stressed the key role of epigenetic alterations such as DNA methylation, histone modification, nucleosome positioning, and the role of small non-coding RNAs in tumourigenic events, disease progression, metastases, and chemoresistance in CRC.[99,100] These epigenetic changes, DNA methylation in selected gene promoters, are the most common and widely investigated molecular alterations associated with human tumours, including CRC.

During methylation, methyl groups are added to cytosine at the 5-position, producing 5-methylcytosine by DNA methyltransferases (DNMT). These cytosine residues are often clustered in CpG islands (CpG islands are short stretches of palindromic DNA with repeated cytosine and guanine nucleotides), which are mostly associated with the promoter regions of most genes.[101,102] Toyota et al[103] reported that methylation of cancer-specific clones was only observed in a subset of colorectal cancers that had a CpG island methylator phenotype (CIMP), while comprehending the global patterns of CpG island methylation in colorectal cancer.

The CpG island methylator phenotype (CIMP) promotes hypermethylation in promoter CpG regions of tumour suppressor genes, causing their inactivation or transcriptional silencing, leading to the development and progression of CRC.[103] Other DNA methylation biomarkers are associated with CRC development of CRC. These epigenetic biomarkers form a useful panel of genes, whose methylation levels form the basis of a useful screening strategy for patients with CRC.

SFRPs

Secreted Frizzled-related proteins (SFRPs) are a family of secreted proteins that are extracellular regulators of the Wnt signalling pathway. Since SFRPs have a cysteine-rich domain (CRD) identical to frizzled receptors, they can bind to these receptors to create inactive complexes that block Wnt signalling.[104] The Wnt antagonists SFRP1 and SFRP2 act as tumour suppressors by interacting with Wnt-1 and Wnt-5 ligands to control the growth and apoptosis of cancer cells. However, abnormal SFRP1 and SFRP2 DNA hypermethylation results in reduced or lost gene expression, inhibition of gene function, and upregulation of the Wnt signalling pathway, all of which contribute to the emergence and development of CRC.[105,106] Cadwell et al[107] showed that SFRP1 mRNA expression was downregulated in 28 (76%) cases out of 51 cases of locally advanced colorectal cancers compared with normal mucosa. Additionally, only 11 of 36 matched normal mucosal samples and 40 of 49 (82%) tumours showed hypermethylation. Similarly, Qi et al[108] observed that SFRP1 mRNA expression was abnormally hypermethylated in adenomas and CRC, unlike in normal mucosal cells. According to Huang et al,[109] SFRP1 and SFRP5 mRNA levels were considerably downregulated in 85 and 80% of CRC, indicating that SFRPs play key roles in tumour progression by inhibiting Wnt signalling. Identification of SFPR2 and SFRP1 methylation in stool samples can detect CRC with good sensitivity and specificity. While SRFP1 stool DNA methylation assay had a sensitivity of 89% and specificity of 86% for diagnosing colorectal neoplasia tumours, SFRP2 stool methylation assay demonstrated sensitivity and specificity of 90% and 77%, respectively.[110]

TFPI2

Another marker that has been shown to undergo aberrant methylation of the promoter CpG islands leading to loss of its expression is tissue factor pathway inhibitor-2 (TFPI-2). A structural homologue of tissue factor pathway inhibitor (TFPI), TFPI-2, is a member of the Kunitz-type serine proteinase inhibitor family. Plasmin, plasma kallikrein, factor XIa, trypsin, and chymotrypsin are serine proteinases that are inhibited by TFPI-2 and the tissue factor/factor VIIa (TF/VIIa) complex.[111,112] It has been reported that abnormal methylation of the TFPI-2 promoter within the CpG island is linked to reduced expression and production of TFPI-2 protein in human malignancies and cancer cell lines.[113] In one such study, TFPI2 methylation was found in stool DNA from patients with stage I to stage III CRC, with a sensitivity of 76% to 89% and a specificity of 79% to 93%. TFPI2 methylation is a frequent and early occurrence in CRCs.[114] Stool DNA testing to identify TFPI2 methylation represents a useful adjunct method for use in conjunction with other non-invasive biomarkers for early CRC screening.[115]

MGMT

O^6-methylguanine DNA methyltransferase (MGMT) is a DNA-repair enzyme. This enzyme also referred as DNA "suicide" repair enzyme plays a key role in repairing damaged guanine nucleotides by removing the alkyl groups from the O^6-position of the guanine, thus acting as an acceptor. This enzyme is essential to avoid gene mutations, cell death, and tumourigenesis caused by alkylating agents.[116,117] When CpG dinucleotides in the MGMT promoter region are methylated, MGMT production is lost, and the enzyme is unable to remove alkyl groups from the methylated guanine.[118] MGMT promoter methylation has been implicated as a frequent and relevant event in CRC cases, and a low expression of MGMT was seen in 27 to 40% of metastatic cases of CRC showing chemoresistance.[119] In a metastatic report by Li et al[12] that incorporated the results of 14 relevant studies, the team concluded that MGMT methylation frequency was much higher in CRC tissues than in normal tissues and that the MGMT promoter was more commonly methylated in CRC patients than in adenoma patients. DNA methylation levels of MGMT serve as a promising screening approach.[120] Stool testing of faecal DNA for methylated genes, including MGMT, represents a simple non-invasive method for screening the early stages of CRC and precancerous lesions.[121] In this study, methylated MGMT was found in 48.1% of patients with CRC and 28.6% of patients with adenoma, respectively, with a 93.7% sensitivity and 77.1% specificity for diagnosing CRC and precancerous lesions.

Vimentin

Vimentin is a type III intermediate filament (IF) protein encoded by VIM. This structural protein is the major cytoskeletal component of mesenchymal cells[122] Vimentin is also employed as a biomarker of cells generated from mesenchyme or cells undergoing epithelial-to-mesenchymal transition (EMT) during both metastatic progression and normal development.[123,124] Aberrant promoter methylation of the vimentin gene linked to the pathogenesis of CRC was reported in a meta-analysis based on seven clinical cohort studies, including a total of 467 CRC subjects.[125] A significantly higher frequency of vimentin promoter methylation in CRC tissues (odds ratio, ie, OR] = 32.41, 95% CI = 21.04 ~ 49.93) than in normal and benign tissues (OR = OR = 1.60, 95% CI 1.05 ~ 2.42) was observed. A similar observation was reported wherein faecal DNA from patients with CRC showed aberrant methylation of exon-1 sequences within the non-transcribed vimentin gene.[126] In this study, vimentin exon-1 sequences were methylated in 83% (38 of 46) and 53% (57 of 107) of tumours from colon cancer patients, thus suggesting that *VMT* gene methylation may also serve as a novel molecular biomarker for colon cancer screening.

In addition to the above genes showing hypermethylation events, studies have reported that hypomethylation of genes is also observed in CRC cases.[127] Hypomethylation of long interspersed nuclear element 1 (LINE-1) is associated with colorectal carcinogenesis.[128,129] Long interspersed nuclear elements (LINEs) refer to a class of non-LTR (long terminal repeat) retrotransposons that are widely distributed in the human genome. They are also referred to as "long interspersed nucleotide elements" or "long interspersed elements". The LINEs account for up to 21.1% of the human genome.[130] In normal somatic cells, LINE-1s are heavily methylated, which restricts the activity of retrotransposal elements and prevents genomic instability.[131] However, global DNA hypomethylation levels are been found to be higher in neoplastic lesions (including hyperplastic polyps and adenomas) than in the normal mucosa.[127] Matsuzaki et al[128] analysed global

LINE-1 methylation levels in 80 sporadic colorectal cancers, 51 adjacent normal tissues, and 20 normal tissues. Results showed that colorectal cancers had significantly lower global methylation levels than did normal tissues (41.0 ± 9.7% versus 54.3 ± 6.5%; $P < 0.001$). Also, tumours with global hypomethylation levels ≤40% had higher number of LOH (+) chromosomal loci unlike seen in tumours without global hypomethylation. This suggests that global hypomethylation plays a role in inducing genomic instability in sporadic CRC. The tumour LINE-1 methylation level may be a useful prognostic biomarker for identifying aggressive carcinomas among MSI CRCs, and the detection of LINE-1 hypomethylation levels in circulating cell-free DNA in plasma represents a potential biomarker for early-stage CRC.[132,133]

Clinical Implications and Advances

In this section, we highlight on the notable advances in the treatment of CRC based on our better understanding of the molecular pathways and identified biomarkers related to the disease progression. One of the major implications of identifying key molecular biomarkers in colorectal cancer (CRC) is "Precision medicine" which is advancing rapidly. This involves tailoring medical treatment to the individual characteristics of each patient, particularly the specific genetic mutations and molecular alterations in their cancer cells.[134] For this, the researchers are exploring the possibility of multigene panel testing to match patients with specific targeted therapies based on their tumor's molecular profile. This approach is being used to develop personalized treatment plans for individual CRC patients, incorporating biomarkers like KRAS, BRAF, MSI, and HER2 status into clinical decision-making.[135]

Other major advancement is the liquid biopsies that are non-invasive tests that detect circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and other molecular components (such as RNA, proteins, and exosomes) from a patient's blood sample.[136] The key biomarkers being detected in ctDNA for CRC include KRAS/NRAS Mutations, BRAF V600E, MSI-H/dMMR mutation, HER2 amplification, etc.[137] The ability of ctDNA will offer advantage in very early detection of adenomas (precancerous polyps) and early carcinomas even before symptoms develop,[138] predicting recurrence rates in patients post-surgery allowing earlier intervention and personalized treatment plans[139] as well as ctDNA levels during treatment (real-time monitoring) may help the physician to monitor the success of ongoing treatment and the need to change to alternative plan.

In addition to the above, the new era of use of artificial intelligence (AI) and machine learning-assisted models represents a major breakthrough in the fight against colorectal cancer.[140,141] Deep learning techniques can integrate multi-omic datasets to identify complex biomarker signatures that may not be detectable through traditional methods. AI algorithms can also predict how CRC patients will respond to certain therapies based on their molecular biomarker profile. In a study by Zhang et al,[142] a machine learning survival predictive system for CRC patients was developed based on their immune prognostic marker profile. Briefly, twenty immune genes were recognized and a prognostic nomogram developed. The prognostic model was able to discriminate between the high-risk patients with poor prognosis from low-risk patients with favourable prognosis, thus predicting the overall survival curves. Thus, machine learning models can forecast responses to immune checkpoint inhibitors by detecting molecular patterns, such as microsatellite instability-high (MSI-H) or tumor mutational burden (TMB). This strategy enhances treatment planning by ensuring that therapies are given primarily to patients who are more likely to benefit from them.[143] Further, the presence of specific mutations in APC, TP53, or PIK3CA can be integrated into predictive algorithms to predict the likelihood of CRC development, recurrence and metastasis.[144,145] Ahmadieh-Yazdi and team[146] investigated CRC metastasis-related biomarkers by employing a machine learning (ML) approach. In this, the team first obtained the gene expression profile of CRC patients with liver metastasis and studied the differentially expressed genes between primary and metastatic samples. Out of the eleven genes selected by machine learning algorithms [Penalized Support Vector Machine (P-SVM) and Least Absolute Shrinkage and Selection Operator (LASSO) algorithms], seven had significant prognostic value in colorectal cancer. Thus, ML algorithms were able to select out and identify a set of potential biomarkers for CRC metastasis essential for timely intervention.

Conclusion

In conclusion, CRC represents a complex and heterogeneous group of disorders at the molecular level, involving multiple signalling pathways. Various trends in genetic mutations and epigenetic changes influence the development and

progression of CRC as well as the way in which it responds to various therapies. Multiple signalling pathways are activated in CRC, making it difficult to address the disease with a single therapy and a single approach. Understanding molecular complexity provides crucial insights that can propel future research and treatment advancements. Detailed molecular profiling will help identify novel biomarkers and actionable mutations in CRC subtypes, leading to personalized treatment regimens that improve efficacy and reduce side effects. This complexity is a valuable source for discovering predictive and prognostic biomarkers, aiding in early diagnosis, treatment monitoring, and response prediction. Investigating resistance-related molecular pathways (eg, Wnt, MAPK) can help develop strategies to overcome treatment resistance. Further, the intra-tumor molecular variability may help identify more effective treatment regimens for metastatic CRC by addressing different clones within the tumor. The study of molecular crosstalk between different pathways (eg, immune evasion, apoptosis) will enable to reveal novel combinations of therapies, optimizing treatment efficacy while minimizing toxicity.

By leveraging the molecular complexity of CRC, future research has the potential to transform treatment approaches, advancing toward more personalized and effective therapies.

Data Sharing Statement

All data are available within the manuscript, and there are no associated data.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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References

1. Xi Y, Xu P. Global colorectal cancer burden in 2020 and projections to 2040. *Transl Oncol*. 2021;14(10):101174. doi:10.1016/j.tranon.2021.101174
2. Colorectal Cancer, CDC. 2020. Available from: https://www.cdc.gov/cancer/colorectal/statistics/index.htm. Accessed September 30, 2024.
3. Summers RM. Polyp size measurement at CT colonography: what do we know and what do we need to know? *Radiology*. 2010;255(3):707–720. doi:10.1148/radiol.10090877
4. Mármol I, Sánchez-de-Diego C, Pradilla Dieste A, Cerrada E, Rodriguez Yoldi MJ. Colorectal carcinoma: a general overview and future perspectives in colorectal cancer. *Int J Mol Sci*. 2017;18(1):197. doi:10.3390/ijms18010197
5. Huang Z, Yang M. Molecular network of colorectal cancer and current therapeutic options. *Front Oncol*. 2022;12:852927. doi:10.3389/fonc.2022.852927
6. Lengauer C, Kinzler KW, Vogelstein B. Genetic instability in colorectal cancers. *Nature*. 1997;386(6625):623–627. doi:10.1038/386623a0
7. Pino MS, Chung DC. The chromosomal instability pathway in colon cancer. *Gastroenterology*. 2010;138(6):2059–2072. doi:10.1053/j.gastro.2009.12.065
8. Thompson SL, Bakhoum SF, Compton DA. Mechanisms of chromosomal instability. *Curr Biol*. 2010;20(6):R285–95. doi:10.1016/j.cub.2010.01.034
9. Siri SO, Martino J, Gottifredi V. Structural chromosome instability: types, origins, consequences, and therapeutic opportunities. *Cancers*. 2021;13(12):3056. doi:10.3390/cancers13123056
10. McKinnon PJ. ATM and ataxia telangiectasia. *EMBO Rep*. 2004;5(8):772–776. doi:10.1038/sj.embor.7400210
11. Takayama O, Yamamoto H, Damdinsuren B, et al. Expression of PPARdelta in multistage carcinogenesis of the colorectum: implications of malignant cancer morphology. *Br J Cancer*. 2006;95(7):889–895. doi:10.1038/sj.bjc.6603343
12. Li XL, Zhou J, Chen ZR, Chng WJ. P53 mutations in colorectal cancer - molecular pathogenesis and pharmacological reactivation. *World J Gastroenterol*. 2015;21(1):84–93. doi:10.3748/wjg.v21.i1.84
13. Shammas MA. Telomeres, lifestyle, cancer, and aging. *Curr Opin Clin Nutr Metab Care*. 2011;14(1):28–34. doi:10.1097/MCO.0b013e32834121b1

14. Maciejowski J, de Lange T. Telomeres in cancer: tumour suppression and genome instability. *Nat Rev Mol Cell Biol*. 2017;18(3):175–186. doi:10.1038/nrm.2016.171
15. Bertorelle R, Rampazzo E, Pucciarelli S, Nitti D, De Rossi A. Telomeres, telomerase and colorectal cancer. *World J Gastroenterol*. 2014;20(8):1940–1950. PMID: 24616570; PMCID: PMC3934464. doi:10.3748/wjg.v20.i8.1940
16. Rampazzo E, Bertorelle R, Serra L, et al. Relationship between telomere shortening, genetic instability, and site of tumour origin in colorectal cancers. *Br J Cancer*. 2010;102(8):1300–1305. doi:10.1038/sj.bjc.6605644
17. Gorbsky GJ. The spindle checkpoint and chromosome segregation in meiosis. *FEBS J*. 2015;282(13):2471–2487. doi:10.1111/febs.13166
18. Potapova T, Gorbsky GJ. The consequences of chromosome segregation errors in mitosis and meiosis. *Biology*. 2017;6(1):12. doi:10.3390/biology6010012
19. Béroud C, Soussi T. APC gene: database of germline and somatic mutations in human tumors and cell lines. *Nucleic Acids Res*. 1996;24(1):121–124. doi:10.1093/nar/24.1.121
20. Aoki K, Taketo MM. Adenomatous polyposis coli (APC): a multi-functional tumor suppressor gene. *J Cell Sci*. 2007;120(Pt 19):3327–3335. doi:10.1242/jcs.03485
21. Senda K, Goi T, Hirono Y, Katayama K, Yamaguchi A. Analysis of RIN1 gene expression in colorectal cancer. *Oncol Rep*. 2007;17(5):1171–1175.
22. Rubinfeld B, Albert I, Porfiri E, Fiol C, Munemitsu S, Polakis P. Binding of GSK3beta to the APC-beta-catenin complex and regulation of complex assembly. *Science*. 1996;272(5264):1023–1026. doi:10.1126/science.272.5264.1023
23. Neufeld KL, Zhang F, Cullen BR, White RL. APC-mediated downregulation of beta-catenin activity involves nuclear sequestration and nuclear export. *EMBO Rep*. 2000;1(6):519–523. doi:10.1093/embo-reports/kvd117
24. Malki A, ElRuz RA, Gupta I, Allouch A, Vranic S, Al Moustafa AE. Molecular mechanisms of colon cancer progression and metastasis: recent insights and advancements. *Int J Mol Sci*. 2020;22(1):130. doi:10.3390/ijms22010130
25. Jass JR, Barker M, Fraser L, et al. APC mutation and tumour budding in colorectal cancer. *J Clin Pathol*. 2003;56(1):69–73. doi:10.1136/jcp.56.1.69
26. Jancík S, Drábek J, Radzioch D, Hajdúch M. Clinical relevance of KRAS in human cancers. *J Biomed Biotechnol*. 2010;2010:150960. doi:10.1155/2010/150960
27. Malumbres M, Barbacid M. RAS oncogenes: the first 30 years. *Nat Rev Cancer*. 2003;3(6):459–465. doi:10.1038/nrc1097
28. Simanshu DK, Nissley DV, McCormick F. RAS proteins and their regulators in human disease. *Cell*. 2017;170(1):17–33. doi:10.1016/j.cell.2017.06.009
29. Porru M, Pompili L, Caruso C, Biroccio A, Leonetti C. Targeting KRAS in metastatic colorectal cancer: current strategies and emerging opportunities. *J Exp Clin Cancer Res*. 2018;37(1):57. doi:10.1186/s13046-018-0719-1
30. Pamonsinlapatham P, Hadj-Slimane R, Lepelletier Y, et al. p120-Ras GTPase activating protein (RasGAP): a multi-interacting protein in downstream signaling. *Biochimie*. 2009;91(3):320–328. doi:10.1016/j.biochi.2008.10.010
31. Meng M, Zhong K, Jiang T, Liu Z, Kwan HY, Su T. The current understanding on the impact of KRAS on colorectal cancer. *Biomed Pharmacother*. 2021;140:111717. doi:10.1016/j.biopha.2021.111717
32. Neumann J, Zeindl-Eberhart E, Kirchner T, Jung A. Frequency and type of KRAS mutations in routine diagnostic analysis of metastatic colorectal cancer. *Pathol Res Pract*. 2009;205(12):858–862. doi:10.1016/j.prp.2009.07.010
33. Arrington AK, Heinrich EL, Lee W, et al. Prognostic and predictive roles of KRAS mutation in colorectal cancer. *Int J Mol Sci*. 2012;13(10):12153–12168. doi:10.3390/ijms131012153
34. Dinu D, Dobre M, Panaitescu E, et al. Prognostic significance of KRAS gene mutations in colorectal cancer--preliminary study. *J Med Life*. 2014;7(4):581–587.
35. Hong DS, Fakih MG, Strickler JH, et al. KRASG12C inhibition with sotorasib in advanced solid tumors. *N Engl J Med*. 2020;383(13):1207–1217. doi:10.1056/NEJMoa1917239.
36. Yaeger R, Weiss J, Pelster MS, et al. Adagrasib with or without cetuximab in colorectal cancer with mutated KRAS G12C. *N Engl J Med*. 2023;388(1):44–54. doi:10.1056/NEJMoa2212419
37. Hagege A, Ambrosetti D, Boyer J, et al. The Polo-like kinase 1 inhibitor onvansertib represents a relevant treatment for head and neck squamous cell carcinoma resistant to cisplatin and radiotherapy. *Theranostics*. 2021;11(19):9571–9586. doi:10.7150/thno.61711
38. Hiraoka K, Inoue T, Taylor RD, et al. Inhibition of KRAS codon 12 mutants using a novel DNA-alkylating pyrrole–imidazole polyamide conjugate. *Nat Commun*. 2015;6:6706. doi:10.1038/ncomms7706
39. Papke B, Murarka S, Vogel HA, et al. Identification of pyrazolopyridazinones as PDEδ inhibitors. *Nat Commun*. 2016;7:11360. doi:10.1038/ncomms11360
40. Jiffry J, Thavornwatanayong T, Rao D, et al. Oncolytic reovirus (pelareorep) induces autophagy in KRAS-mutated colorectal cancer. *Clin Cancer Res*. 2021;27(3):865–876. doi:10.1158/1078-0432.CCR-20-2385
41. Goel S, Ocean AJ, Parakrama RY, et al. Elucidation of pelareorep pharmacodynamics in A Phase I trial in patients with KRAS-mutated colorectal cancer. *Mol Cancer Ther*. 2020;19(5):1148–1156. doi:10.1158/1535-7163.MCT-19-1117
42. Ross SJ, Revenko AS, Hanson LL, et al. Targeting KRAS-dependent tumors with AZD4785, a high-affinity therapeutic antisense oligonucleotide inhibitor of KRAS. *Sci Transl Med*. 2017;9(394):eaal5253. doi:10.1126/scitranslmed.aal5253
43. Bennouna J, Lang I, Valladares-Ayerbes M, et al. A Phase II, open-label, randomised study to assess the efficacy and safety of the MEK1/2 inhibitor AZD6244 (ARRY-142886) versus capecitabine monotherapy in patients with colorectal cancer who have failed one or two prior chemotherapeutic regimens. *Invest New Drugs*. 2011;29(5):1021–1028. doi:10.1007/s10637-010-9392-8
44. Vogelstein B, Lane D, Levine AJ. Surfing the p53 network. *Nature*. 2000;408(6810):307–310. doi:10.1038/35042675
45. Olivier M, Hollstein M, Hainaut P. TP53 mutations in human cancers: origins, consequences, and clinical use. *Cold Spring Harb Perspect Biol*. 2010;2(1):a001008. doi:10.1101/cshperspect.a001008
46. Sionov RV, Hayon IL, Haupt Y. The regulation of p53 growth suppression. In: *Madame Curie Bioscience Database* [Internet]. Austin (TX): Landes Bioscience; 2013.
47. Chen J. The cell-cycle arrest and apoptotic functions of p53 in tumor initiation and progression. *Cold Spring Harb Perspect Med*. 2016;6(3):a026104. doi:10.1101/cshperspect.a026104

48. Brooks CL, Gu W. p53 ubiquitination: Mdm2 and beyond. *Mol Cell*. 2006;21(3):307–315. doi:10.1016/j.molcel.2006.01.020
49. Zandi R, Selivanova G, Christensen CL, Gerds TA, Willumsen BM, Poulsen HS. PRIMA-1Met/APR-246 induces apoptosis and tumor growth delay in small cell lung cancer expressing mutant p53. *Clin Cancer Res*. 2011;17(9):2830–2841. doi:10.1158/1078-0432.CCR-10-3168
50. Ryan KM, Phillips AC, Vousden KH. Regulation and function of the p53 tumor suppressor protein. *Curr Opin Cell Biol*. 2001;13:332–337.doi. doi:10.1016/S0955-0674(00)00216-7
51. Russo A, Bazan V, Iacopetta B, Kerr D, Soussi T, Gebbia N; TP53-CRC Collaborative Study Group. The TP53 colorectal cancer international collaborative study on the prognostic and predictive significance of p53 mutation: influence of tumor site, type of mutation, and adjuvant treatment. *J Clin Oncol*. 2005;23(30):7518–7528. doi:10.1200/JCO.2005.00.471
52. Rivlin N, Brosh R, Oren M, Rotter V. Mutations in the p53 tumor suppressor gene: important milestones at the various steps of tumorigenesis. *Genes Cancer*. 2011;2(4):466–474. doi:10.1177/1947601911408889
53. Iacopetta B. TP53 mutation in colorectal cancer. *Hum Mutat*. 2003;21(3):271–276. doi:10.1002/humu.10175
54. Rangel LP, Ferretti GDS, Costa CL, et al. p53 reactivation with induction of massive apoptosis-1 (PRIMA-1) inhibits amyloid aggregation of mutant p53 in cancer cells. *J Biol Chem*. 2019;294(10):3670–3682. doi:10.1074/jbc.RA118.004671
55. Azmi AS, Philip PA, Beck FW, et al. MI-219-zinc combination: a new paradigm in MDM2 inhibitor-based therapy. *Oncogene*. 2011;30 (1):117–126. doi:10.1038/onc.2010.403
56. Shen H, Maki CG. Pharmacologic activation of p53 by small-molecule MDM2 antagonists. *Curr Pharm Des*. 2011;17(6):560–568. doi:10.2174/138161211795222603
57. Issaeva N, Bozko P, Enge M, et al. Small molecule RITA binds to p53, blocks p53-HDM-2 interaction and activates p53 function in tumors. *Nat Med*. 2004;10(12):1321–1328. doi:10.1038/nm1146
58. Ueno T, Endo S, Saito R, et al. The sirtuin inhibitor tenovin-6 upregulates death receptor 5 and enhances cytotoxic effects of 5-fluorouracil and oxaliplatin in colon cancer cells. *Oncol Res*. 2013;21(3):155–164. doi:10.3727/096504013X13854886566598
59. Reyes-Zurita FJ, Pachón-Peña G, Lizárraga D, Rufino-Palomares EE, Cascante M, Lupiáñez JA. The natural triterpene maslinic acid induces apoptosis in HT29 colon cancer cells by a JNK-p53-dependent mechanism. *BMC Cancer*. 2011;11:154. doi:10.1186/1471-2407-11-154
60. Cordero-Herrera I, Martín MA, Bravo L, Goya L, Ramos S. Epicatechin gallate induces cell death via p53 activation and stimulation of p38 and JNK in human colon cancer SW480 cells. *Nutr Cancer*. 2013;65(5):718–728. PMID: 23859040. doi:10.1080/01635581.2013.795981
61. Yoo TH, Lee JH, Chun HS, Chi SG. α-Lipoic acid prevents p53 degradation in colon cancer cells by blocking NF-κB induction of RPS6KA4. *Anticancer Drugs*. 2013;24(6):555–565. doi:10.1097/CAD.0b013e32836181eb
62. Neitzel C, Seiwert N, Göder A, et al. Lipoic acid synergizes with antineoplastic drugs in colorectal cancer by targeting p53 for proteasomal degradation. *Cells*. 2019;8(8):794. doi:10.3390/cells8080794
63. Kirley SD, D'Apuzzo M, Lauwers GY, Graeme-Cook F, Chung DC, Zukerberg LR. The cables gene on chromosome 18Q regulates colon cancer progression in vivo. *Cancer Biol Ther*. 2005;4(8):861–863. doi:10.4161/cbt.4.8.1894
64. Wu CL, Kirley SD, Xiao H, Chuang Y, Chung DC, Zukerberg LR. Cables enhances cdk2 tyrosine 15 phosphorylation by Wee1, inhibits cell growth, and is lost in many human colon and squamous cancers. *Cancer Res*. 2001;61(19):7325–7332.
65. Park DY, Sakamoto H, Kirley SD, et al. The cables gene on chromosome 18q is silenced by promoter hypermethylation and allelic loss in human colorectal cancer. *Am J Pathol*. 2007;171(5):1509–1519. doi:10.2353/ajpath.2007.070331
66. Arnason T, Pino MS, Yilmaz O, et al. Cables1 is a tumor suppressor gene that regulates intestinal tumor progression in Apc(Min) mice. *Cancer Biol Ther*. 2013;14(7):672–678. doi:10.4161/cbt.25089
67. Tarafa G, Villanueva A, Farré L, et al. DCC and SMAD4 alterations in human colorectal and pancreatic tumor dissemination. *Oncogene*. 2000;19(4):546–555. doi:10.1038/sj.onc.1203353
68. Keino-Masu K, Masu M, Hinck L, et al. Deleted in colorectal cancer (DCC) encodes a netrin receptor. *Cell*. 1996;87(2):175–185. doi:10.1016/s0092-8674(00)81336-7
69. Takagi Y, Kohmura H, Futamura M, et al. Somatic alterations of the DPC4 gene in human colorectal cancers in vivo. *Gastroenterology*. 1996;111(5):1369–1372. doi:10.1053/gast.1996.v111.pm8898652
70. Woodford-Richens KL, Rowan AJ, Gorman P, et al. SMAD4 mutations in colorectal cancer probably occur before chromosomal instability, but after divergence of the microsatellite instability pathway. *Proc Natl Acad Sci U S A*. 2001;98(17):9719–9723. doi:10.1073/pnas.171321498
71. Fujimura T, Ohta T, Oyama K, Miyashita T, Miwa K. Role of cyclooxygenase-2 in the carcinogenesis of gastrointestinal tract cancers: a review and report of personal experience. *World J Gastroenterol*. 2006;12(9):1336–1345. doi:10.3748/wjg.v12.i9.1336
72. Negi RR, Rana SV, Gupta V, et al. Over-expression of cyclooxygenase-2 in colorectal cancer patients. *Asian Pac J Cancer Prev*. 2019;20 (6):1675–1681. doi:10.31557/APJCP.2019.20.6.1675
73. Gurram B, Zhang S, Li M, et al. Celecoxib conjugated fluorescent probe for identification and discrimination of cyclooxygenase-2 enzyme in cancer cells. *Anal Chem*. 2018;90(8):5187–5193. doi:10.1021/acs.analchem.7b05337
74. Sawhney M, Rohatgi N, Kaur J, et al. Expression of NF-kappaB parallels COX-2 expression in oral precancer and cancer: association with smokeless tobacco. *Int J Cancer*. 2007;120(12):2545–2556. doi:10.1002/ijc.22657
75. Wu QB, Sun GP. Expression of COX-2 and HER-2 in colorectal cancer and their correlation. *World J Gastroenterol*. 2015;21(20):6206–6214. doi:10.3748/wjg.v21.i20.6206
76. Buskens CJ, Van Rees BP, Sivula A, et al. Prognostic significance of elevated cyclooxygenase 2 expression in patients with adenocarcinoma of the esophagus. *Gastroenterology*. 2002;122(7):1800–1807. doi:10.1053/gast.2002.33580
77. Oshima M, Dinchuk JE, Kargman SL, et al. Suppression of intestinal polyposis in Apc delta716 knockout mice by inhibition of cyclooxygenase 2 (COX-2). *Cell*. 1996;87(5):803–809. doi:10.1016/s0092-8674(00)81988-1
78. Chandrasekharan NV, Simmons DL. The cyclooxygenases. *Genome Biol*. 2004;5(9):241. doi:10.1186/gb-2004-5-9-241
79. Wang D, Dubois RN. Eicosanoids and cancer. *Nat Rev Cancer*. 2010;10(3):181–193. doi:10.1038/nrc2809
80. Mizuno R, Kawada K, Sakai Y. Prostaglandin E2/EP signaling in the tumor microenvironment of colorectal cancer. *Int J Mol Sci*. 2019;20 (24):6254. doi:10.3390/ijms20246254
81. Lala PK, Nandi P, Majumder M. Roles of prostaglandins in tumor-associated lymphangiogenesis with special reference to breast cancer. *Cancer Metastasis Rev*. 2018;37(2–3):369–384. doi:10.1007/s10555-018-9734-0

82. Karpisheh V, Joshi N, Zekiy AO, et al. EP4 receptor as a novel promising therapeutic target in colon cancer. *Pathol Res Pract*. 2020;216 (12):153247. doi:10.1016/j.prp.2020.153247
83. Szweda M, Rychlik A, Babińska I, Pomianowski A. Significance of cyclooxygenase-2 in oncogenesis. *J Vet Res*. 2019;63(2):215–224. doi:10.2478/jvetres-2019-0030
84. Li GM. Mechanisms and functions of DNA mismatch repair. *Cell Res*. 2008;18(1):85–98. doi:10.1038/cr.2007.115
85. Nojadeh JN, Behrouz Sharif S, Sakhinia E. Microsatellite instability in colorectal cancer. *EXCLI J*. 2018;17:159–168. doi:10.17179/excli2017-948
86. Boland CR, Goel A. Microsatellite instability in colorectal cancer. *Gastroenterology*. 2010;138(6):2073–2087.e3. doi:10.1053/j.gastro.2009.12.064
87. Sinicrope FA. DNA mismatch repair and adjuvant chemotherapy in sporadic colon cancer. *Nat Rev Clin Oncol*. 2010;7(3):174–177. doi:10.1038/nrclinonc.2009.235
88. Sinicrope FA, Sargent DJ. Molecular pathways: microsatellite instability in colorectal cancer: prognostic, predictive, and therapeutic implications. *Clin Cancer Res*. 2012;18(6):1506–1512. doi:10.1158/1078-0432.CCR-11-1469
89. Hampel H, Frankel WL, Martin E, et al. Feasibility of screening for Lynch syndrome among patients with colorectal cancer. *J Clin Oncol*. 2008;26(35):5783–5788. doi:10.1200/JCO.2008.17.5950
90. Popat S, Hubner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. *J Clin Oncol*. 2005;23 (3):609–618. doi:10.1200/JCO.2005.01.086
91. Boland CR, Thibodeau SN, Hamilton SR, et al. A national cancer institute workshop on microsatellite instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. *Cancer Res*. 1998;58(22):5248–5257.
92. Jass JR, Young J, Leggett BA. Biological significance of microsatellite instability-low (MSI-L) status in colorectal tumors. *Am J Pathol*. 2001;158(2):779–781. doi:10.1016/s0002-9440(10)64020-5
93. Ribic CM, Sargent DJ, Moore MJ, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N Engl J Med*. 2003;349(3):247–257. doi:10.1056/NEJMoa022289
94. Koi M, Umar A, Chauhan DP, et al. Human chromosome 3 corrects mismatch repair deficiency and microsatellite instability and reduces N-methyl-N'-nitro-N-nitrosoguanidine tolerance in colon tumor cells with homozygous hMLH1 mutation. *Cancer Res*. 1994;54(16):4308–4312.
95. Pocard M, Bras-Gonçalves R, Hamelin R, Northover J, Poupon MF. Response to 5-fluorouracil of orthotopically xenografted human colon cancers with a microsatellite instability: influence of P53 status. *Anticancer Res*. 2000;20(1A):85–90. PMID: 10769638.
96. Kang S, Na Y, Joung SY, Lee SI, Oh SC, Min BW. The significance of microsatellite instability in colorectal cancer after controlling for clinicopathological factors. *Medicine*. 2018;97(9):e0019. doi:10.1097/MD.0000000000010019
97. Jass JR. Classification of colorectal cancer based on correlation of clinical, morphological and molecular features. *Histopathology*. 2007;50 (1):113–130. doi:10.1111/j.1365-2559.2006.02549.x
98. Yamagishi H, Kuroda H, Imai Y, Hiraishi H. Molecular pathogenesis of sporadic colorectal cancers. *Chin J Cancer*. 2016;35:4. doi:10.1186/s40880-015-0066-y
99. Bennett RL, Licht JD. Targeting Epigenetics in Cancer. *Annu Rev Pharmacol Toxicol*. 2018;58:187–207. doi:10.1146/annurev-pharmtox-010716-105106
100. Lu Y, Chan YT, Tan HY, Li S, Wang N, Feng Y. Epigenetic regulation in human cancer: the potential role of epi-drug in cancer therapy. *Mol Cancer*. 2020;19(1):79. doi:10.1186/s12943-020-01197-3
101. Jabbari K, Bernardi G. CpG doublets, CpG islands and Alu repeats in long human DNA sequences from different isochore families. *Gene*. 1998;224(1–2):123–127. doi:10.1016/s0378-1119(98)00474-0
102. Breiling A, Lyko F. Epigenetic regulatory functions of DNA modifications: 5-methylcytosine and beyond. *Epigenet Chromatin*. 2015;8:24. doi:10.1186/s13072-015-0016-6
103. Toyota M, Ahuja N, Ohe-Toyota M, Herman JG, Baylin SB, Issa JP. CpG island methylator phenotype in colorectal cancer. *Proc Natl Acad Sci U S A*. 1999;96(15):8681–8686. doi:10.1073/pnas.96.15.8681
104. Miranda M, Morici JF, Zanoni MB, Bekinschtein P. Brain-derived neurotrophic factor: a key molecule for memory in the healthy and the pathological brain. *Front Cell Neurosci*. 2019;13:363. doi:10.3389/fncel.2019.00363
105. Surana R, Sikka S, Cai W, et al. Secreted frizzled related proteins: implications in cancers. *Biochim Biophys Acta*. 2014;1845(1):53–65. doi:10.1016/j.bbcan.2013.11.004
106. Kalmár A, Péterfia B, Hollósi P, et al. DNA hypermethylation and decreased mRNA expression of MAL, PRIMA1, PTGDR and SFRP1 in colorectal adenoma and cancer. *BMC Cancer*. 2015;15:736. doi:10.1186/s12885-015-1687-x
107. Yu J, Xie Y, Li M, et al. Association between SFRP promoter hypermethylation and different types of cancer: a systematic review and meta-analysis. *Oncol Lett*. 2019;18(4):3481–3492. doi:10.3892/ol.2019.10709
108. Caldwell GM, Jones C, Gensberg K, et al. The Wnt antagonist sFRP1 in colorectal tumorigenesis. *Cancer Res*. 2004;64(3):883–888. doi:10.1158/0008-5472.can-03-1346
109. Qi J, Zhu YQ, Luo J, Tao WH. Hypermethylation and expression regulation of secreted frizzled-related protein genes in colorectal tumor. *World J Gastroenterol*. 2006;12(44):7113–7117. doi:10.3748/wjg.v12.i44.7113
110. Huang D, Yu B, Deng Y, et al. SFRP4 was overexpressed in colorectal carcinoma. *J Cancer Res Clin Oncol*. 2010;136(3):395–401. doi:10.1007/s00432-009-0669-2
111. Sprecher CA, Kisiel W, Mathewes S, Foster DC. Molecular cloning, expression, and partial characterization of a second human tissue-factor-pathway inhibitor. *Proc Natl Acad Sci U S A*. 1994;91(8):3353–3357. doi:10.1073/pnas.91.8.3353
112. Ota Y, Koizume S, Nakamura Y, et al. Tissue factor pathway inhibitor-2 is specifically expressed in ovarian clear cell carcinoma tissues in the nucleus, cytoplasm and extracellular matrix. *Oncol Rep*. 2021;45(3):1023–1032. doi:10.3892/or.2021.7944
113. Sierko E, Wojtukiewicz MZ, Kisiel W. The role of tissue factor pathway inhibitor-2 in cancer biology. *Semin Thromb Hemost*. 2007;33 (7):653–659. doi:10.1055/s-2007-991532
114. Glöckner SC, Dhir M, Yi JM, et al. Methylation of TFPI2 in stool DNA: a potential novel biomarker for the detection of colorectal cancer. *Cancer Res*. 2009;69(11):4691–4699. doi:10.1158/0008-5472.CAN-08-0142

115. Zhang W, Yang C, Wang S, et al. SDC2 and TFPI2 methylation in stool samples as an integrated biomarker for early detection of colorectal cancer. *Cancer Manag Res*. 2021;33:3601–3617. PMID: 33958894; PMCID: PMC8096344. doi:10.1055/s-2007-991532
116. Natarajan AT, Vermeulen S, Darroudi F, et al. Chromosomal localization of human O6-methylguanine-DNA methyltransferase (MGMT) gene by in situ hybridization. *Mutagenesis*. 1992;7(1):83–85. doi:10.1093/mutage/7.1.83
117. Sharma S, Salehi F, Scheithauer BW, Rotondo F, Syro LV, Kovacs K. Role of MGMT in tumor development, progression, diagnosis, treatment and prognosis. *Anticancer Res*. 2009;29(10):3759–3768.
118. Inno A, Fanetti G, Di Bartolomeo M, et al. Role of MGMT as biomarker in colorectal cancer. *World J Clin Cases*. 2014;2(12):835–839. doi:10.12998/wjcc.v2.i12.835
119. Esteller M, Herman JG. Generating mutations but providing chemosensitivity: the role of O6-methylguanine DNA methyltransferase in human cancer. *Oncogene*. 2004;23(1):1–8. doi:10.1038/sj.onc.1207316
120. Raut JR, Guan Z, Schrotz-King P, Brenner H. Fecal DNA methylation markers for detecting stages of colorectal cancer and its precursors: a systematic review. *Clin Clin Epigenet*. 2020;12(1):122. doi:10.1186/s13148-020-00904-7
121. Huang ZH, Li LH, Yang F, Wang JF. Detection of aberrant methylation in fecal DNA as a molecular screening tool for colorectal cancer and precancerous lesions. *World J Gastroenterol*. 2007;13(6):950–954. PMID: 17352030; PMCID: PMC4065936. doi:10.3748/wjg.v13.i6.950
122. Battaglia RA, Delic S, Herrmann H, Snider NT. Vimentin on the move: new developments in cell migration. *F1000Res*. 2018; 7: F1000FacultyRev–1796. doi:10.12688/f1000research.15967.1
123. Satelli A, Li S. Vimentin in cancer and its potential as a molecular target for cancer therapy. *Cell Mol Life Sci*. 2011;68(18):3033–3046. doi:10.1007/s00018-011-0735-1
124. Usman S, Waseem NH, Nguyen TKN, et al. Vimentin is at the heart of epithelial mesenchymal transition (EMT) mediated metastasis. *Cancers*. 2021;13(19):4985. doi:10.3390/cancers13194985
125. Li YW, Kong FM, Zhou JP, Dong M. Aberrant promoter methylation of the vimentin gene may contribute to colorectal carcinogenesis: a meta-analysis. *Tumour Biol*. 2014;35(7):6783–6790. doi:10.1007/s13277-014-1905-1
126. Chen WD, Han ZJ, Skoletsky J, et al. Detection in fecal DNA of colon cancer-specific methylation of the nonexpressed vimentin gene. *J Natl Cancer Inst*. 2005;97(15):1124–1132. doi:10.1093/jnci/dji204
127. Bariol C, Suter C, Cheong K, et al. The relationship between hypomethylation and CpG island methylation in colorectal neoplasia. *Am J Pathol*. 2003;162(4):1361–1371. doi:10.1016/S0002-9440(10)63932-6
128. Matsuzaki K, Deng G, Tanaka H, Kakar S, Miura S, Kim YS. The relationship between global methylation level, loss of heterozygosity, and microsatellite instability in sporadic colorectal cancer. *Clin Cancer Res*. 2005;11(24 Pt 1):8564–8569. doi:10.1158/1078-0432.CCR-05-0859
129. Sunami E, de Maat M, Vu A, Turner RR, Hoon DS. LINE-1 hypomethylation during primary colon cancer progression. *PLoS One*. 2011;6(4): e18884. doi:10.1371/journal.pone.0018884
130. Rodić N, Burns KH. Long interspersed element-1 (LINE-1): passenger or driver in human neoplasms? *PLoS Genet*. 2013;9(3):e1003402. doi:10.1371/journal.pgen.1003402
131. Hoffmann MJ, Schulz WA. Causes and consequences of DNA hypomethylation in human cancer. *Biochem Cell Biol*. 2005;83(3):296–321. PMID: 15959557. doi:10.1139/o05-036
132. Inamura K, Yamauchi M, Nishihara R, et al. Tumor LINE-1 methylation level and microsatellite instability in relation to colorectal cancer prognosis. *J Natl Cancer Inst*. 2014;106(9):dju195. doi:10.1093/jnci/dju195
133. Nassar FJ, Msheik ZS, Nasr RR, et al. Methylated circulating tumor DNA as a biomarker for colorectal cancer diagnosis, prognosis, and prediction. *Clin Epigenet*. 2021;13:111. doi:10.1186/s13148-021-01095-5
134. Riedesser JE, Ebert MP, Betge J. Precision medicine for metastatic colorectal cancer in clinical practice. *Ther Adv Med Oncol*. 2022;14:17588359211072703. doi:10.1177/17588359211072703
135. Crutcher M, Waldman S. Biomarkers in the development of individualized treatment regimens for colorectal cancer. *Front Med*. 2022;9:1062423. doi:10.3389/fmed.2022.1062423
136. Armakolas A, Kotsari M, Koskinas J. Liquid biopsies, novel approaches and future directions. *Cancers*. 2023;15(5):1579. doi:10.3390/cancers15051579
137. Gutierrez ME, Price KS, Lanman RB, et al. Genomic Profiling for *KRAS, NRAS, BRAF*, microsatellite instability, and mismatch repair deficiency among patients with metastatic colon cancer. *JCO Precis Oncol*. 2019;3:PO.19.00274. doi:10.1200/PO.19.00274
138. Mo S, Dai W, Wang H, et al. Early detection and prognosis prediction for colorectal cancer by circulating tumour DNA methylation haplotypes: a multicentre cohort study. *EClinicalMedicine*. 2022;55:101717. doi:10.1016/j.eclinm.2022.101717
139. Krell M, Llera B, Brown ZJ. Circulating tumor DNA and management of colorectal cancer. *Cancers*. 2023;16(1):21. doi:10.3390/cancers16010021
140. Mitsala A, Tsalikidis C, Pitiakoudis M, Simopoulos C, Tsaroucha AK. Artificial intelligence in colorectal cancer screening, diagnosis and treatment. a new era. *Curr Oncol*. 2021;28(3):1581–1607. doi:10.3390/curroncol28030149
141. Yang J, Huang J, Han D, Ma X. Artificial intelligence applications in the treatment of colorectal cancer: a narrative review. *Clin Med Insights Oncol*. 2024;18:11795549231220320. doi:10.1177/11795549231220320
142. Zhang Z, Huang L, Li J, Wang P. Bioinformatics analysis reveals immune prognostic markers for overall survival of colorectal cancer patients: a novel machine learning survival predictive system. *BMC Bioinf*. 2022;23(1):124. doi:10.1186/s12859-022-04657-3
143. Gustav M, Reitsam NG, Carrero ZI, et al. Deep learning for dual detection of microsatellite instability and POLE mutations in colorectal cancer histopathology. *NPJ Precis Oncol*. 2024;8(1):115. doi:10.1038/s41698-024-00592-z
144. Li AJ, Li HG, Tang EJ, et al. PIK3CA and TP53 mutations predict overall survival of stage II/III colorectal cancer patients. *World J Gastroenterol*. 2018;24(5):631–640. doi:10.3748/wjg.v24.i5.631.
145. Zheng S, He H, Zheng J, et al. Machine learning-based screening and validation of liver metastasis-specific genes in colorectal cancer. *Sci Rep*. 2024;14(1):17679. doi:10.1038/s41598-024-68706-y
146. Ahmadieh-Yazdi A, Mahdavinezhad A, Tapak L, Nouri F, Taherkhani A, Afshar S. Using machine learning approach for screening metastatic biomarkers in colorectal cancer and predictive modelling with experimental validation. *Sci Rep*. 2023;13(1):19426. doi:10.1038/s41598-023-46633-8

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