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Genetics and Epigenetics of Colorectal Cancer: An Extensive Review

Suneha Rani¹, Khushbhu Meena², Krishankant Kushwaha³

¹Assistant Professor, School of Pharmaceutical Sciences, SGRRU, Dehradun(Uttarakhand), sunehadeshwal13@gmail.com

²PhD, Scholar,Cbmr Sgpgi Campus Lucknow, khushaboomeena1@gmail.com

³Assistant Professor, Rajasthan Pharmacy College, Ajmer road, Bhankarota, Jaipur, Rajasthan 302026, krishankantkushwahagsits@gmail.com

ABSTRACT: One of the most prevalent and fatal malignancies in the world is colorectal cancer (CRC). Invasive adenocarcinoma develops thru a series of steps in which normal colonic epithelial cells progressively undergo genetic and epigenetic alterations. Chromosome destabilization (CIN), normal microsatellite instability (MSI) brought on by flaws in the DNA repair mismatch system, and, in a smaller percentage of cases, an abnormally mutated phenotype linked to alterations in the validation domains of POLE or POLD1 are the three main types of genomic instability that are primarily linked to colorectal cancer (CRC). Colorectal carcinogenesis is significantly influenced by epigenetic modifications in addition to these hereditary ones. Widespread DNA hypomethylation, aberrant hypermethylation of tumor-suppressor and mismatch-repair gene promoter regions, the CpG insula methylator phenotype (CIMP), changes in histone modifications, interference with chromatin-remodeling mechanisms, and aberrant regulation of non-coding RNAs are some of these. The onset, development, and biological variety of colorectal cancer are all influenced by these hereditary and epigenetic aberrations.

INTRODUCTION:

Colorectal cancer (CRC) remains one of the most commonly diagnosed cancers and a major contributor to cancer-related mortality worldwide. Of particular concern is the increasing incidence of CRC among individuals younger than 50 years, which has received considerable attention in recent years. The development of CRC is generally a gradual process that occurs over several years and commonly follows the well-established adenoma–carcinoma sequence.¹ During this progression, normal colonic mucosa undergoes a series of morphological and molecular changes, beginning with the formation of a benign adenomatous polyp, followed by the development of an adenoma with high-grade dysplasia, and eventually progressing to invasive carcinoma. This stepwise transformation is driven by the gradual accumulation of somatic genetic alterations involving oncogenes, tumor-suppressor genes, and genes responsible for maintaining genomic integrity.²

The interaction and accumulation of these molecular changes ultimately promote the initiation, progression, and invasive behaviour of colorectal tumours. It is currently widely recognized that genetic abnormalities are not the exclusive cause of colorectal cancer. Tumor cells have persistent modifications in gene regulation, such as DNA methylation, chromatin remodeling, histone modifications, and regulation of non-coding RNAs, in addition to genetic changes. Rather than merely being secondary occurrences, these epigenetic modifications are becoming recognized as essential elements of colorectal tumor biology that communicate with genetic anomalies and can impact one another throughout tumor growth. In-depth genomic and methylation research results, together with developments in single-cell transcriptome analysis, have demonstrated that genetic and epigenetic changes simultaneously affect tumor-cell properties and interactions in the tumor microenvironment.³

1. THE GENETIC ASSOCIATION OF COLORECTAL CANCER:

Chromosome disruption (CIN), microsatellite dysfunction (MSI), and an abnormally mutated phenotype linked to flaws in DNA polymerase proofreading activity are the three main and physiologically separate types of genomic instability that lead to colorectal cancer (CRC). There may be some overlap between these routes, despite the fact that they can be differentiated based on their underlying molecular features.⁴ The serrated pathway, which has unique morphological characteristics and is often linked to epigenetic changes, is another route of colorectal carcinogenesis added to these traditional channels. Because genetic and epigenetic modifications frequently interact throughout the formation and progression of serrated colorectal lesions, this route is particularly relevant to the epigenetic processes covered later in this study.

1.1 The Pathway of Chromosomal Instability (CIN):

The most common kind of genomic instability seen in sporadic colorectal tumors (CRCs) is chromosomal instability (CIN). Aneuploidy, structural chromosomal changes, and loss of heterozygosity (LOH) are among the several chromosomal abnormalities that define it. These genetic anomalies frequently coexist with the gradual accumulation of changes in important driving genes, which together contribute to the development and spread of colorectal tumors.⁵

1.1.1 Dysregulation associated with the Wnt Signaling Pathway Mediated by APC:

One of the first and most significant molecular events in the formation of the majority of sporadic colorectal cancers resulting from the chromosome instability (CIN) cellular pathway is that to be the atypical biallelic silencing of the intestinal polyposis coli (APC) tumor-suppressor gene. Family-associated and adenomatous polyposis syndrome (FAP), a hereditary disorder linked to a significantly elevated risk of colorectal cancer, is also caused by germline mutations in APC. Under normal circumstances, APC helps manage Wnt signaling by regulating and degrading β -catenin.⁶ When this regulating process is disrupted by the loss of functioning APC, β -catenin builds up and moves into the nucleus, where it activates Wnt-responsive genes that encourage colonic epithelial cell growth. Disruption of APC function—or, perhaps less commonly, a direct activating modification in β -catenin—is considered a crucial triggering event in colorectal carcinogenesis since continuous Wnt network activation is implicated across various phases of CIN-pathway tumor growth.⁷

1.1.2 KRAS and BRAF in the RAS/RAF/MAPK Transmission Pathway:

About one-third to almost half of colorectal tumors have activating mutations in KRAS, with codons 12 and 13 having the most prevalent changes and codons 61, 117, and 146 having less frequent mutations. Rather than in the early phases of tumor growth, these mutations typically appear during the change between an adenoid lesion to carcinoma. Because mutant KRAS is constantly active, the downstream MAPK signaling pathway is continuously stimulated, supporting the growth and survival of tumor cells. Because KRAS mutations are linked to a poor outcome following anti-EGFR monoclonal antibody treatment, their presence is very significant clinically.⁸ Therefore, determining the status of RAS mutations is a crucial step in molecular testing prior to starting anti-EGFR therapy. A unique genetic category of colorectal cancer is characterized by BRAF changes, especially the V600E mutant, which are typically incompatible with KRAS mutations. These tumors are more common in the right side of the colon and are generally linked to the jagged pathway of colorectal carcinogenesis. A poor prognosis is also linked to BRAF-mutated colorectal tumors, especially in individuals with metastatic disease. Significantly, BRAF V600E mutations are often seen in conjunction with genomic instability-high (MSI-H) status and sporadic MLH1 promoter hypermethylation, underscoring the intimate connection between BRAF-driven tumor formation and epigenetic changes.⁹

1.1.3 TP53:

A significant terminal occurrence in the chromosomal instability (CIN) route of colorectal cancer formation is mutations in TP53, the coding region encoding the tumor-suppressor protein p53. Such modifications, which can result from deletion or mutation, are frequently linked to an adenoma's development into an aggressive carcinoma. Under normal circumstances, p53 induces apoptosis in cells with substantial DNA damage and functions as a crucial regulator of cell-cycle checkpoints. These defense systems are compromised when TP53 activity is reduced, enabling cells with accumulated genetic and chromosomal defects to avoid apoptosis and cell-cycle arrest. Because of this, genetically unstable cells are able to persist and multiply, which contributes to the aneuploidy and chromosomal abnormalities that are typical of the CIN phenotype.¹⁰

1.1.4 TGF- β /SMAD Pathway:

A significant molecular event in the development of colorectal cancer is the inactivation of essential elements of the TGF- β

signaling pathway, including SMAD4 as well as the type II TGF- β transmitter (TGFBR2). Microsatellite instability (MSI)-positive tumors, where frameshift mutations found within coding microsatellite areas might impair receptor function, are particularly prone to TGFBR2 changes. Under normal circumstances, TGF- β signaling serves as a crucial growth-inhibitory pathway that aids in controlling colonic epithelial cell proliferation. Tumor invasion and development are facilitated by the loss of this regulating function, which permits unchecked cellular proliferation. Additionally, these changes have been linked to worse clinical outcomes and more aggressive illness.¹¹

1.2 The Microsatellite Instability (MSI) Pathway:

The DNA mismatch repair (MMR) mechanism, which mainly includes the MLH1, MSH2, MSH6, and PMS2 genes, is impaired in 10–15% of colorectal tumors (CRC). These proteins normally recognize and fix mistakes that occur during DNA replication. Replication mistakes are unrepaired and gradually build up whilst MMR function is compromised, especially in repeated DNA sequences called microsatellites. With mutation rates frequently surpassing 10–100 mutations per megabase, this leads to a highly warped or hypermutated genomic condition.¹² Defective mismatch repair (dMMR) frameshift mutations can result in aberrant peptide sequences called neoantigens, which the immune system recognizes as alien. As a result, dMMR/MSI-high colorectal tumors frequently show a robust immune response, which is typified by a significant infiltration of tumor-infiltrating lymphocytes (TILs). Because these tumors typically have a very favorable response to conventional immune checkpoint blockers, as covered in Section 6, this increased immunogenicity is clinically significant.¹³

1.3 Mutated Molecular tumor types: POLD1 and POLE:

Mutations influencing the standard exonuclease or proofing regions for the DNA polymerases POLE and POLD1 are that to be present in about 3% of colorectal tumors. Due to these changes, the polymerases' usual proofreading function is compromised, which leads to a high tumor mutational load that may surpass that of MSI-high malignancies by enabling a huge number of replication mistakes to accumulate. These ultramutated colorectal malignancies are often highly immunogenic and may elicit a potent antitumor immune response, much like dMMR/MSI-high tumors. Nevertheless, tumors with POLE/POLD1 mutations are a unique genetic subtype that develop via a different mechanism than mismatch-repair failure.¹⁴

1.4 The Pathway of Radiated Neoplasia:

Instead of the traditional adenoma–carcinoma sequence, sessile scalloped lesions (SSLs) represent a significant alternative route of CRC (colorectal carcinoma) development. Early BRAF mutations, distinctive serrated morphological traits, and a strong propensity for the CpG region methylator phenotype (CIMP) are frequently linked to this serrated pathway. In a subset of instances, excessive methylation may cause MLH1 promoter silencing as the lesion advances, ultimately leading to the formation of MSI-high cancer. As a result, the serrated pathway offers a striking illustration of the intimate relationship among genetic and epigenetic changes in the early phases of colorectal carcinogenesis, showing how both biological processes may coexist and jointly affect the development of tumors.¹⁵

2. EPIGENOMICS MODIFICATIONS IN COLORECTAL CANCER:

In addition to genetic changes, epigenetic mechanisms—which entail persistent and possibly heritable modifications to gene expression without changing the underlying DNA sequence—are now that to play a key role in the development of colorectal cancer (CRC). DNA methylation, histone changes, chromatin remodeling, and the control of gene transcription by non-coding RNAs are the main epigenetic mechanisms implicated in colorectal cancer. When taken as a whole, these processes can change the activity and expression of genes related to DNA repair, cell division, proliferation, and tumor growth, which can lead to colorectal carcinogenesis.¹⁶

2.1 Global Norm Hypomethylation:

When compared to normal colorectal mucosa, the genomes of colorectal cancer (CRC) frequently show a significant decrease in DNA methylation throughout repetitious genomic areas and gene bodies. By compromising the structural stability of both centromeric and pericentromeric heterochromatin and encouraging the reactivation of usually quiet transposable elements, this widespread DNA hypomethylation is that to lead to genomic and chromosomal instability. Crucially, as colorectal lesions advance from adenoma to invasive carcinoma, the degree of global hypomethylation appears to rise throughout tumor

formation.¹⁷

2.2 Promoter Hypermethylation and the CpG Island Methylator Phenotype (CIMP):

The CpG island methylator phenotype (CIMP-high) is a molecular pattern associated with widespread and coordinated hypermethylation across numerous CpG-island regions in a subset of colorectal tumors. BRAF V600E mutations, unstable precursor lesions, advanced age, and a prevalence of right-sided or proximal colonic placement are usually linked to these tumors. Tumors frequently display a sporadic MSI-high phenotype when CIMP is combined with methylation-mediated silencing of MLH1.¹⁸ Sporadic mismatch-repair failure is mostly caused by hypermethylation of the MLH1 promoter. Differentiating this acquired mutation from hereditary MMR mutations linked to Lynch syndrome is crucial since the two disorders have very distinct consequences for family screening, genetic counseling, and monitoring. MLH1 methylation testing and/or BRAF mutation analysis can be used in clinical practice to distinguish Lynch syndrome from random MSI-high CRC.¹⁹

2.3 Other Methylation-Silenced Genes:

Promoter hypermethylation can inactivate MLH1 as well as a number of different genes involved in cellular control and colorectal tumor suppression. These include genes that participate in DNA restoration and cell-cycle regulation, as well as genes that adversely control the Wnt signaling pathway, such those in the SFRP family. The discovery of these abnormally methylated enzymes has also aided in the creation of molecular biomarkers used for the diagnosis of colorectal cancer. For instance, methylation markers including SDC2, SEPT9, and NDRG4, coupled with additional methylated loci, have been included to diagnostic tests based on blood and stool that are intended to make non-surgical colorectal cancer screening and diagnosis easier.²⁰

3. HISTONE VARIATIONS:

Without changing the DNA sequence, itself, histone proteins go thru a number of post-translational changes, such as the following: acetylation, normal methylation, phosphorylation, amplification, and ubiquitination, which are crucial for modulating gene expression and chromatin structure. Histone mutation patterns have been shown to alter early in the development of colorectal cancer (CRC).²¹ For instance, CRC is often associated with decreased levels of histone H4 lysine 16 acetylation (H4K16ac) and H4 lysine 20 trimethylation (H4K20me3). Tumor growth may also be exacerbated by aberrant activity of the enzymes that control these alterations, such as histone deacetylases (HDACs) and histone methyltransferases like EZH2. For example, EZH2 stimulates H3K27 trimethylation, which represses genes related to apoptosis, cellular differentiation, and tumor suppression. Crucially, DNA methylation and histone alterations work together.²²

3.1 Complexes of Chromatin Remodeling:

In a subset of colorectal tumors, components of the SWI/SNF remodeling chromatin complex, most notably ARID1A, are often altered or deleted. This disrupts nucleosome placement at regulatory regions and contributes to dysregulated transcriptional programs. Loss of ARID1A levels has been associated with more aggressive tumor behavior and, in certain situations, altered susceptibility to immune-based and targeted therapy; this is a topic of ongoing research.²³

3.2 Non-coding RNA:

Short non-coding RNAs known as microRNAs (miRNAs) are widely dysregulated in colorectal cancer (CRC) and post-transcriptionally inhibit target messenger RNAs. While some, like a majority of the miR-34 and let-7 families, act as tumor suppressors and are frequently silenced, frequently thru promoter hypermethylation of their host genes, others, like miR-21, are oncomiRs that promote tumor growth, invasion, and chemoresistance and are often overexpressed.²⁴ Similarly, dysregulated, long non-coding RNAs (lncRNAs) like CRNDE and CCAT1 are linked to the transcription, proliferation, and metastasis of the Wnt pathway. In addition to DNA-methylation-based liquid biopsy panels, circulating miRNA signatures are being investigated as less invasive diagnostics for early identification and prognosis.²⁵

3.3 The Theory of Genome-Epigenome Co-Evolution:

It has been demonstrated by recent integration studies that look at both genetic and epigenetic changes within a single colorectal tumor showing these changes do not happen separately. Rather, specific mutations and patterns of DNA methylation may emerge at distinct phases of clonal proliferation, and genetic mutations and epigenetic modifications may

coexist and impact one another during tumor evolution.²⁶ The concept of epigenetic modifications has changed as a result of these discoveries; they are now thought to be actively and selectively maintained aspects of tumor formation rather than just secondary effects of genetic abnormalities. Understanding the molecular variety of colorectal cancer (CRC), improving tumor categorization, and elucidating how colorectal tumors may develop resistance to anticancer treatments are all significantly impacted by this intimate relationship between genetic and epigenetic mechanisms.²⁷

4. BIO-CHEMICAL TAXONOMY OF COLORECTAL CANCER:

Initiatives to transition from histological staging to molecular categorization have been motivated by the realization that CIN and MSI mechanisms, together with the epigenetic states they are linked to, result in tumors with significantly different biology.²⁸

4.1 TCGA Classification of Genomes:

By analyzing tumor genomes mostly at the DNA level, the Cancer Genome Atlas, or TCGA, research offered significant findings regarding the genetic landscape of colorectal cancer. CRCs were broadly categorized into three major groups based on their genomic characteristics: a hypermutated subgroup that primarily corresponded to defective mismatch correction (dMMR)/microsatellite instability-high (MSI-H) tumors; a much smaller ultramutated subgroup that was characterized by mutations in the POLE or POLD1 exonuclease domains; and a larger group of tumors that showed chromosomal instability (CIN). The main genetic pathways underpinning the molecular variety of colorectal cancer were identified with the use of this categorization.²⁹

4.2 Molecular Subtypes of Consensus (CMS):

An international research partnership created a classification method that divided colorectal cancer (CRC) into four different Consensus Molecular Subtypes (CMS) using extensive gene expression data from thousands of colorectal tumor samples. A more thorough foundation for comprehending the differing characteristics of colorectal cancer is provided by the unique molecular characteristics, biological processes, and clinical behavior patterns that define each subtype. Table 1 provides an overview of these four kinds.³⁰

Table 1: Molecular subtypes of consensus³¹

S. No	Subtype	Frequency	Key Features	Clinical Association
01.	CMS I (MSI- IMMUNE)	~14%	Substantial immune response and activation, BRAF mutant enrichment, MSI-high, hypermutated	Good prognosis in the early stages; checkpoint treatment response
02.	CMS II (The CANNONIC system)	~37%	WNT and MYC signaling activity, high chromosomal instability, and epithelial phenotype	Best overall survival; anti-EGFR/bevacizumab-based treatments may be beneficial
03.	CMS III (METABOLIC standard)	~13%	Metabolic dysregulation, KRAS mutation enrichment, low copy-number change, and mixed MSI status	Outlook: moderate
04.	CMS IV (Mesenchymal sclerosis)	~23%	Features of the epithelial-mesenchymal transition, angiogenesis, TGF- β activation, and stromal infiltration	Poorest overall and relapse-free survival; irinotecan-based regimens may help

4.3 Significant Developments: Superior Integration of CRIS with iCMS:

The molecular profiles of CMS represent expression of gene signals from a combination of normal cytokines, stromal components, and malignant epithelial cells since the categorization is centered on bulk tumor tissue. Subsequent classification methods have concentrated on determining the molecular characteristics inherent to the tumor epithelium in order to overcome this constraint. For instance, the Colorectal Intrinsic Subtypes (CRIS) categorization method uses computational minimization of the contribution of stromal and immunological signals to designate five distinct subtypes (CRIS-A to CRIS-E). A more straightforward intrinsic categorization consisting of two primary epithelial subgroups, iCMS2 and iCMS3, which more precisely reflect tumor-cell-intrinsic biology, has been proposed more recently by single-cell transcriptome investigations.³² In contrast, the iCMS3 genotype is seen in a significant percentage of microsatellite-stable malignancies but is also highly linked to dMMR/MSI tumors. This result implies that mismatch-repair deficit may not be the sole transcriptional program linked to MSI. Together, these incremental improvements show the continuous endeavor to differentiate molecular signals originating from the surrounding tumor microenvironment from genetic and epigenetic programs unique to tumor cells.⁴⁰

5. BIOMARKER-BASED METHODS FOR DIAGNOSIS AND SCREENING:

The emergence of least-invasive biomarker-based methods that may supplement current colonoscopy-based screening techniques has been prompted by the early and frequent emergence of genetic alterations and, in specific, epigenetic changes during colorectal carcinogenesis. In addition to KRAS detection of mutations and circulating tumor DNA (ctDNA) analysis, blood- and bowel-based assays that incorporate hydrogenated DNA markers, including an SDC2, SEPT9, and NDRG4, have demonstrated excellent diagnostic performance for identifying both advanced precancerous lesions and established colorectal cancer.⁴ These epigenetic and liquid-biopsy methods may offer helpful screening alternatives for both average-risk and high-risk individuals, and recent systematic studies indicate that they have significant promise for increasing early detection.³⁹

6. INTEGRATING EPIGENETIC AND GENETIC ASPECTS FOR TARGETED THERAPY:

6.1 Biochemical Applicant Selection for Anti-EGFR Treatment:

Colorectal tumors with wild-type RAS status, comprising both KRAS and NRAS, respond well to monoclonal antibodies targeting epidermal growth factor receptors (EGFR), namely cetuximab and panitumumab. Because tumors with RAS changes typically do not respond to an anti-EGFR treatment, these medicines are chosen only once molecular testing has verified the lack of activating RAS mutations. Therefore, before choosing anti-EGFR therapy for individuals with metastatic colorectal cancer, RAS mutation analysis and BRAF testing are crucial parts of molecular profiling.³⁸

6.2 Therapeutic Targeting of KRAS Alterations:

In light of its great affinity for GTP and comparatively smooth molecular surface, KRAS was once thought to be a challenging therapeutic target, which hindered the creation of potent direct inhibitors. However, this treatment landscape has significantly shifted with the advent of covalent inhibitors that target the KRAS G12C mutation. The combination of sotorasib and panitumumab and adagrasib and cetuximab has shown clinically significant efficacy in treated individuals with KRAS - mutated G12C metastatic colorectal cancer and has been approved by regulators. However, reaction rates involving these combination techniques are still poor and often lower than those found in lung cancer with a KRAS G12C mutation.²⁹ The significant significance of EGFR signaling in colorectal cancer, which can foster adaptive resistance after KRAS G12C suppression, is primarily responsible for this discrepancy.³⁷ However, because only a tiny percentage of KRAS-mutated colorectal tumors are caused by KRAS G12C, current research is concentrating more on creating treatments for more prevalent mutations, including KRAS G12D and KRAS G12V.³¹ Simultaneously, more comprehensive approaches to blocking various RAS variations are being studied, such as medicines that can target the active GTP-bound form of RAS. A number of these pan-RAS and next-generation strategies are in the early stages of clinical development and might broaden the application of KRAS-directed treatment for colorectal carcinoma.³⁴

6.3 Inhibition of Immune Checkpoints in dMMR/MSI-High Cancer of the Colon:

Immune checkpoint inhibition is especially vulnerable to dMMR/MSI-high colorectal malignancies because mismatch-repair deficit is linked to a high tumor mutational load and enhanced neoantigen generation. When compared to traditional

chemotherapy, pembrolizumab has shown better progression-free survival and greater objective response rates among patients with dMMR/MSI-high tumors in the metastatic scenario.⁶ In certain patient categories, combination therapies that target each of the PD-1 and CTLA-4 mechanisms have also demonstrated improved response rates. As a result, immune checkpoint inhibitors are now a crucial first-line therapeutic option for metastatic dMMR/MSI-high colorectal cancer, which includes tumors linked to Lynch syndrome as well as spontaneous malignancies caused by hypermethylation of the MLH1 promoter. These results demonstrate the direct application of molecular changes found thru tumor profiling to treatment decision-making. Crucially, an epigenetic mechanism—specifically, hypermethylation of the MLH1 promoter—may be the cause of the underlying MMR-deficient phenotype, underscoring the clinical significance of epigenetic changes in precision therapy approaches.³⁴

6.4 A Focus on Genomic Disorder in Colorectal Cancer:

Therapeutic approaches targeted at altering aberrant epigenetic states have drawn a lot of attention in colorectal cancer (CRC) because epigenetic changes may be reversible. Histone deacetylase inhibitors and DNA methyltransferase inhibitors, such as azacitidine and decitabine, have been studied in an effort to overcome resistance to traditional chemotherapy or immunotherapy and ³⁵restore the presentation of epigenetically silenced tumor-suppressor genes.⁹ However, they have often shown little clinical efficacy as stand-alone treatments for colorectal cancer. Therefore, combination techniques are becoming more and more important in current research, especially the utilization of epigenetic treatments as a type of tumor priming prior to immune checkpoint inhibition. Microsatellite-stable tumors, which are often more immunogenic and have demonstrated limited response to immunotherapy alone, are of special relevance for this approach.³⁶

7. PREDICTIVE ANALYSIS AND PREDICTION-BASED IMPORTANCE:

Beyond diagnostic and treatment choice, genetic and epigenetic changes in colorectal carcinoma have consequences since a number of molecular characteristics can offer crucial prognostic information. The BRAF V600E mutant is linked to worse survival rates in metastatic colorectal cancer, especially in microsatellite-stable tumors.⁶ Likewise, different clinical outcomes and clinical trajectories are linked to CIMP-high status, mismatch-resistant status, and the CMS4 (mesenchymal) subtype. Furthermore, the initial tumor's anatomical location—often referred to as its right or left-sidedness—has become a significant predictor and prognostic factor. Because tumor sidedness is intimately linked to the transportation of underlying genetic and physiologic subtypes and can thus affect both prognosis and treatment response, this difference is very important.¹⁰

8. RECENT PERSPECTIVES AND OPPORTUNITIES FOR DEVELOPMENT:

8.1 Cell-specific and spatial multi-omics: Using both single-cell and geographic multi-omic technologies will allow for more accurate characterization of genetic and epigenetic programs intrinsic to tumor cells while differentiating them from signals originating from the underlying vascular and immune microenvironment. These methods could get around several significant drawbacks of bulk-tissue-based CMS categorization.³⁵

8.2 Extension of KRAS-targeted therapies: It is anticipated that future therapeutic development will go beyond inhibition of KRAS G12C to include wider RAS(ON)-directed inhibitors and more common changes, namely KRAS G12D and G12V. Research into adaptive resistance mechanisms unique to colorectal cancer will continue to be a top emphasis.⁶

8.3 Clinical use of CMS classification: The integration of molecular subtyping into regular clinical practice may be aided by additional development, clinical validation, and standardization of FFPE-friendly, immunohistochemistry-derived, and image-based CMS classifiers.¹⁰

8.4 Integration of immunotherapy and epigenetic therapy: Individuals with microsatellite-fixed colorectal cancer, who typically react poorly compared to checkpoint blockade alone, may benefit from immunotherapy if epigenetic-modifying drugs are combined with immune checkpoint inhibitors.¹²

9. CONCLUSION:

It is becoming more well acknowledged that colorectal cancer is a complex illness that results from the interaction of epigenetic and genetic changes as opposed to from a straightforward buildup of mutations alone. Tumor start and development, the immunological microenvironment, and variations in treatment response are all influenced by these interrelated molecular mechanisms. Epigenetic systems involving histone modifications, DNA methylation, chromatin

remodeling, and non-coding RNA control coexist alongside major genetic pathways such as chromosomal instability, a microsatellite instability, and ultra-mutation. Crucially, spontaneous hypermethylation of the MLH1 promoter and the ensuing mismatch-repair deficit are examples of how epigenetic changes can also result in functionally important molecular states. Our appreciation of colorectal cancer morphology has been reinforced by the incorporation of these molecular findings into categorization frameworks like the Generally Accepted Molecular Subtypes Model (CMS) and their ensuing modifications.

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