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Proliferation And Prognostic Biomarkers In Colorectal Cancer

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Abstract

Colorectal cancer (CRC) is a major cause of morbidity and mortality worldwide. Despite advances in diagnosis and therapy, CRC remains a heterogeneous disease with diverse clinical outcomes. A growing body of evidence suggests that tumor proliferation dynamics and associated molecular alterations play critical roles in disease progression, recurrence, and treatment response. This review summarizes recent progress in understanding proliferation-related biomarkers in CRC, emphasizing the prognostic and predictive value of immunohistochemical and molecular indicators. Classical proliferation markers such as Ki-67, PCNA, and cyclins are discussed alongside genetic and epigenetic alterations including APC, KRAS, TP53 mutations, microsatellite instability (MSI), chromosomal instability (CIN), and CpG island methylator phenotype (CIMP). The integration of immunohistochemistry with next-generation sequencing and RNA profiling has enabled identification of novel prognostic factors, including non-coding RNAs and methylation signatures. Understanding these markers enhances risk stratification and supports the development of personalized treatment approaches in colorectal cancer management.

Keywords

colorectal cancer; proliferation; biomarkers; Ki-67; PCNA; cyclins; molecular pathways; immunohistochemistry; MSI; CIN; prognosis

1. Introduction

Colorectal cancer (CRC) ranks among the most prevalent malignancies globally, accounting for approximately 10% of all cancer cases and representing the second leading cause of cancer-related mortality (Sung et al., 2023). The global burden of CRC continues to rise due to changing lifestyles, aging populations, and limited access to early detection programs. Although advances in screening, surgical techniques, and systemic therapies have improved survival rates, a substantial proportion of patients experience disease recurrence or progression. To improve clinical outcomes, researchers are increasingly focusing on molecular and immunohistochemical biomarkers that reflect tumor biology more accurately than conventional staging systems. Tumor proliferation is one of the essential hallmarks of cancer (Hanahan, 2022). Quantitative evaluation of proliferative activity in CRC provides crucial prognostic and predictive information. Traditional markers such as Ki-67 and PCNA have long been used to assess tumor growth fraction, but their prognostic significance remains controversial due to methodological variability and tumor heterogeneity. Recent studies highlight that integrating these markers with molecular indicators—including APC, KRAS, TP53, and MSI status—can yield more precise prognostic models. Furthermore, epigenetic and transcriptional regulators such as non-coding RNAs and methylation patterns have emerged as powerful predictors of disease progression and treatment response. This review aims to provide a comprehensive analysis of proliferation-related prognostic biomarkers in CRC, focusing on the transition from immunohistochemistry to molecular biology approaches and their clinical relevance.

2. Molecular Mechanisms of Colorectal Carcinogenesis

Colorectal carcinogenesis is a complex, multistep process driven by genetic, epigenetic, and microenvironmental alterations that transform normal mucosal cells into malignant adenocarcinoma. The classical model, proposed by Fearon and Vogelstein (1990), describes sequential accumulation of mutations in key oncogenes and tumor suppressor genes, including APC, KRAS, TP53, and SMAD4. These changes activate proliferative signaling, disrupt apoptosis, and promote chromosomal instability (CIN). Alternative

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molecular routes, such as microsatellite instability (MSI) and CpG island methylator phenotype (CIMP), define distinct biological subtypes of colorectal cancer (Toyota et al., 1999; Guinney et al., 2015). Together, these mechanisms underlie the remarkable heterogeneity of CRC in morphology, clinical behavior, and treatment response.

Table 1. Major molecular pathways in colorectal cancer and their characteristics:

Pathway	Main Genetic Events	Molecular Mechanism	Frequency in CRC	Clinical Relevance
Chromosomal Instability (CIN)	APC, KRAS, TP53, SMAD4	Aneuploidy, loss of heterozygosity	70–85%	Associated with poor differentiation and prognosis
Microsatellite Instability (MSI)	MLH1, MSH2, MSH6, PMS2	Defective DNA mismatch repair	≈15%	Better prognosis, immunotherapy-sensitive
CpG Island Methylator Phenotype (CIMP)	MLH1, p16, BRAF	Promoter hypermethylation and gene silencing	15–20%	Linked to serrated pathway and BRAF mutations

The interplay between these pathways defines the molecular landscape of CRC. Chromosomal instability is the most prevalent mechanism, promoting aneuploidy and copy-number variations. MSI results from defective mismatch repair (MMR) genes and is associated with increased tumor immunogenicity. CIMP involves widespread promoter methylation, leading to epigenetic silencing of tumor-suppressor genes such as MLH1 and CDKN2A. Each pathway is characterized by unique histopathological features and distinct therapeutic implications.

3. Cell Proliferation Models in Colorectal Cancer

Tumor proliferation in CRC reflects complex interactions between genetic mutations, cellular signaling, and the tumor microenvironment. Historically, the growth kinetics of CRC have been explained by two major frameworks: the somatic mutation theory (SMT) and the tissue organization field theory (TOFT). The SMT suggests that proliferation results from accumulated mutations in oncogenes and tumor suppressor genes, while TOFT emphasizes disruption of the normal tissue microenvironment as the primary cause of cancer initiation (Soto & Sonnenschein, 2018). In colorectal cancer, both theories converge, as continuous Wnt/β-catenin and MAPK pathway activation promotes uncontrolled cell division. Cancer stem cells (CSCs) play a pivotal role in this process. Subpopulations expressing stemness markers such as LGR5, CD44, and ALDH1 demonstrate enhanced self-renewal and therapy resistance (de Sousa e Melo et al., 2017; Li et al., 2021). These CSCs can remain quiescent for long periods, contributing to disease recurrence after chemotherapy or radiotherapy. Furthermore, dysregulated cell-cycle checkpoints involving cyclin-dependent kinases (CDKs) and their inhibitors (p21, p27) further drive tumor growth and genomic instability. Understanding these models is crucial for identifying prognostic biomarkers that accurately represent tumor proliferation and therapeutic vulnerability.

4. Immunohistochemical Proliferation Markers

Immunohistochemistry (IHC) remains one of the most widely used methods for assessing proliferative activity in colorectal cancer (CRC) because it is reproducible, affordable, and easily applicable to archival tissue. Proliferation-related proteins reflect tumor aggressiveness, recurrence potential, and treatment sensitivity. Among them, **Ki-67**, **proliferating cell nuclear antigen (PCNA)**, **cyclins (A, B1, D1, E)**, and **thymidylate**

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synthase (TS) are the most thoroughly investigated. Each corresponds to distinct phases of the cell cycle and carries specific prognostic implications.

4.1 Ki-67

Ki-67 is a nuclear antigen expressed during all active cell-cycle phases (G_1–M) but absent in quiescent (G_0) cells. It therefore serves as a reliable index of cellular proliferation. Numerous studies have shown that a high Ki-67 labeling index (LI) correlates with poor differentiation, higher TNM stage, and reduced overall and disease-free survival (Yang et al., 2020; Li & Wang, 2022). However, some reports indicate that elevated Ki-67 may mark tumors more responsive to chemotherapy. Discrepancies stem from non-standardized antibodies, scoring methods, and cut-off thresholds. Despite this variability, Ki-67 remains a useful component of multiparametric prognostic panels.

4.2 Proliferating Cell Nuclear Antigen (PCNA)

PCNA is a 36 kDa nuclear protein functioning as an auxiliary factor for DNA polymerase δ during DNA replication and repair. Its expression peaks in late G_1 and S phases, making it an excellent indicator of active DNA synthesis. PCNA overexpression occurs in ≈ 90 % of CRC cases and is associated with lymph-node metastasis, vascular invasion, and shorter DFS (Zhou et al., 2020). Because PCNA also participates in DNA-repair processes, it is not a purely proliferative marker; however, combined Ki-67/PCNA assessment improves prediction of relapse and overall survival.

4.3 Cyclins (A, B1, D1, E)

Cyclins regulate transitions between cell-cycle phases through activation of cyclin-dependent kinases (CDKs).

- **Cyclin A2** controls the S→G_2 transition and is overexpressed in about 80 % of CRC cases; high expression correlates with poor DFS and OS (Bahnassy et al., 2019).
- **Cyclin B1** mediates entry into mitosis; while elevated in primary tumors, its reduction in metastases suggests a dual role—driving proliferation yet restraining migration (Chen et al., 2022).
- **Cyclin D1**, induced via Wnt/β-catenin and KRAS signaling, promotes G_1/S progression and is linked to early recurrence and unfavorable DFS (Maeda et al., 2021).
- **Cyclin E** initiates DNA replication and is commonly up-regulated in poorly differentiated CRCs (Zheng et al., 2021).

Taken together, cyclin dysregulation reflects key oncogenic events controlling cell-cycle acceleration and therapeutic resistance.

4.4 Thymidylate Synthase (TS)

Thymidylate synthase catalyzes the methylation of dUMP to dTMP, providing nucleotides for DNA synthesis and serving as the main target of fluoropyrimidine-based chemotherapy (5-FU, capecitabine). Elevated TS expression in CRC correlates with resistance to 5-FU regimens and reduced OS (Badary et al., 2023). Conversely, low TS levels predict better response and survival. Because TS expression can differ between primary and metastatic lesions, parallel evaluation of both sites is advisable when planning systemic therapy.

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Table 2. Summary of major immunohistochemical proliferation markers and their prognostic implications in colorectal cancer

Marker	Function / Pathway	Typical Expression in CRC	Prognostic Trend	Clinical Implication
Ki-67	Nuclear proliferation index	High in 60–80 % cases	High → shorter OS/DFS (variable)	General proliferation indicator
PCNA	DNA polymerase δ cofactor	Overexpressed in 60–90 %	High → poor prognosis	Predicts relapse with Ki-67
Cyclin A2	Controls S/G_2 transition	Overexpressed (~80 %)	High → worse DFS/OS	Independent unfavorable factor
Cyclin D1	Drives G_1/S transition	Overexpressed (50–70 %)	High → early recurrence / poor DFS	Therapeutic target (CDK4/6 inhibitors)
Cyclin E	Initiates DNA replication	High in poorly differentiated tumors	High → aggressive behavior	Used with Ki-67 for risk stratification
TS	Catalyzes dTMP synthesis	Variable (↑ → chemoresistance)	High → poor OS/DFS (5-FU resistance)	Predicts response to fluoropyrimidines

Summary:
Collectively, IHC proliferation markers supply vital information on tumor behavior and prognosis. Ki-67 and PCNA serve as general indicators of proliferation, while cyclins and TS unveil mechanistic details of cell-cycle control and drug sensitivity. Their combined use strengthens predictive power and supports individualized CRC management.

5. Molecular and Genetic Prognostic Biomarkers in Colorectal Cancer

The genetic framework of colorectal cancer (CRC) is characterized by multiple driver mutations that promote uncontrolled proliferation, invasion, and metastasis. The most frequently altered genes—**APC, KRAS, BRAF, TP53, and SMAD4**—constitute the molecular foundation of CRC progression and therapeutic response (Kasprzak, 2023; Guinney et al., 2015).

5.1 APC and Wnt/β-Catenin Signaling

The adenomatous polyposis coli (**APC**) gene is inactivated in approximately 70–80 % of sporadic CRCs, representing an early event in the adenoma–carcinoma sequence (Fearon & Vogelstein, 1990). Loss of APC function causes cytoplasmic accumulation of β-catenin, which translocates to the nucleus and activates transcription of proliferation-related genes such as MYC and CCND1. Elevated nuclear β-catenin expression correlates with poor differentiation and worse survival (Zhou et al., 2022).

5.2 KRAS and BRAF Mutations

KRAS mutations occur in roughly 40 % of CRCs and activate the MAPK and PI3K/AKT pathways, enhancing cell-cycle progression and chemoresistance (Yoshino et al., 2022). BRAF mutations, predominantly V600E, are detected in 10–15 % of CRCs and frequently co-occur with CIMP-positive or MSI-high tumors. BRAF-mutated CRC is associated with right-sided location, mucinous morphology, and poor prognosis (Rowland et al., 2021). Because KRAS or BRAF alterations confer primary resistance to anti-EGFR monoclonal antibodies, their detection is essential for therapeutic decision-making.

5.3 TP53 and SMAD4 Alterations

Mutations in TP53 appear in 50–60 % of advanced CRCs and are considered late events in tumor evolution (Kasprzak, 2023). Inactivation of p53 leads to defective apoptosis and genomic instability. Co-loss of SMAD4, a central mediator of TGF-β signaling, further enhances tumor invasiveness and correlates with

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increased metastatic potential (Sjöblom et al., 2020). Dual TP53/SMAD4 alterations therefore mark aggressive CRC phenotypes.

5.4 Microsatellite Instability (MSI)

MSI results from inactivation of mismatch-repair (MMR) genes—MLH1, MSH2, MSH6, and PMS2—and characterizes about 15 % of CRCs (Boland & Goel, 2022). MSI-high (MSI-H) tumors accumulate insertion–deletion mutations in repetitive DNA tracts, producing frameshift neoantigens that trigger strong immune responses. Clinically, MSI-H CRC is associated with better overall survival and dramatic responsiveness to immune-checkpoint inhibitors targeting PD-1 or PD-L1 (Overman et al., 2021).

5.5 Chromosomal Instability (CIN)

CIN, the most common molecular pathway in CRC (≈ 70 % of cases), involves large-scale chromosomal gains and losses, aneuploidy, and loss of heterozygosity (Lee et al., 2021). CIN-positive tumors often show poor differentiation, frequent TP53 mutations, and resistance to conventional chemotherapy. Quantification of aneuploidy burden is emerging as an independent predictor of recurrence risk.

5.6 CpG Island Methylator Phenotype (CIMP)

CIMP-positive CRC exhibits widespread promoter hypermethylation, leading to epigenetic silencing of tumor-suppressor genes such as MLH1 and p16INK4a (Issa, 2014). CIMP commonly overlaps with BRAF mutations and the serrated neoplasia pathway. Clinically, it indicates intermediate prognosis and potential responsiveness to demethylating therapies (Yamamoto et al., 2023).

Table 3. Major Molecular and Genetic Biomarkers in Colorectal Cancer

Biomarker / Pathway	Mechanism / Target	Frequency in CRC	Prognostic Trend	Clinical Utility
APC / β-Catenin	Wnt signaling activation	70–80 %	Poor differentiation, early driver	Early detection, risk stratification
KRAS	MAPK, PI3K/AKT activation	35–45 %	Chemoresistance, shorter OS	Excludes anti-EGFR therapy
BRAF (V600E)	MAPK pathway	10–15 %	Aggressive, poor OS	Target for BRAF/MEK inhibitors
TP53	Cell-cycle arrest, apoptosis	50–60 %	Advanced stage, poor prognosis	Prognostic, possible therapeutic target
SMAD4	TGF-β signaling	15–20 %	Promotes metastasis	Predictor of relapse risk
MSI-H	MMR deficiency	≈ 15 %	Better OS, immune-responsive	Guides immunotherapy use
CIN	Aneuploidy, LOH	70 %	Poor OS, chemoresistance	Prognostic marker
CIMP	Promoter hypermethylation	17–20 %	Intermediate prognosis	Diagnostic for serrated pathway

Summary:

The integration of molecular and genetic biomarkers provides a refined framework for CRC classification and prognosis. MSI-H and CIMP subtypes generally display improved outcomes and unique therapeutic vulnerabilities, whereas CIN-driven and TP53/KRAS-mutated tumors exhibit aggressive behavior and limited treatment response. Routine molecular testing is now indispensable for precision oncology in colorectal cancer.

6. Non-Coding RNAs and Epigenetic Regulation in Colorectal Cancer

Beyond classical genetic mutations, colorectal carcinogenesis is profoundly influenced by **non-coding RNAs (ncRNAs)** and **epigenetic mechanisms** that regulate gene expression without altering the DNA sequence.

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The interplay between microRNAs (miRNAs), long non-coding RNAs (lncRNAs), DNA methylation, and histone modification represents a dynamic network shaping tumor proliferation, invasion, and chemoresistance (Liu et al., 2021).

6.1 MicroRNAs (miRNAs)

MicroRNAs are small, single-stranded RNAs (~22 nucleotides) that suppress translation of target mRNAs. Aberrant miRNA expression is a hallmark of CRC.

- **miR-21** is one of the most consistently upregulated oncogenic miRNAs ("oncomiRs") in CRC. It targets PTEN and PDCD4, leading to enhanced proliferation and invasion (Toiyama et al., 2022). Elevated miR-21 levels in plasma and tissue strongly correlate with poor overall survival and early recurrence, making it a promising non-invasive biomarker.
- **miR-34a**, a downstream effector of p53, acts as a tumor suppressor by repressing BCL2 and SIRT1. Its downregulation is associated with chemoresistance and advanced stage (Yan et al., 2021).
- The **miR-200 family** (miR-200a/b/c, miR-141, miR-429) maintains epithelial identity by inhibiting epithelial–mesenchymal transition (EMT). Loss of these miRNAs promotes metastasis and poor prognosis (Fang et al., 2020).

6.2 Long Non-Coding RNAs (lncRNAs)

LncRNAs (>200 nucleotides) regulate chromatin remodeling, transcription, and post-transcriptional processing. Several lncRNAs are now recognized as key proliferation regulators in CRC.

- **HOTAIR** (HOX transcript antisense RNA) interacts with the PRC2 complex to repress tumor-suppressor genes via histone H3K27 methylation. Its overexpression predicts metastasis and unfavorable survival (Wang et al., 2022).
- **MALAT1** (Metastasis-associated lung adenocarcinoma transcript 1) enhances cell-cycle progression through the PI3K/AKT pathway and correlates with lymph-node metastasis (Zhang et al., 2021).
- **CCAT1** (Colon cancer-associated transcript 1), located near the MYC gene, promotes Wnt/β-catenin activation and cellular proliferation (Kim et al., 2023).

6.3 DNA Methylation and Histone Modifications

Aberrant **DNA methylation** is one of the earliest and most stable epigenetic alterations in CRC. Global hypomethylation contributes to chromosomal instability, whereas promoter hypermethylation silences key tumor-suppressor genes (MLH1, p16INK4a, CDH1). **Histone modifications**, including acetylation and methylation, alter chromatin accessibility. For example, overexpression of histone deacetylases (HDAC1/2) promotes proliferation, while inhibitors of HDACs show therapeutic potential (Zhou et al., 2023).

Table 4. Non-coding RNA biomarkers and their prognostic implications in colorectal cancer

Biomarker	Type / Function	Expression Pattern	Prognostic Trend	Clinical Application
miR-21	OncomiR; inhibits PTEN, PDCD4	Upregulated	Poor OS/DFS, early recurrence	Diagnostic plasma biomarker
miR-34a	Tumor suppressor, p53 target	Downregulated	Poor OS, chemoresistance	Predicts 5-FU response
miR-200 family	EMT suppressor	Downregulated	Promotes metastasis, poor OS	Marker of EMT and metastasis
HOTAIR	lncRNA, chromatin modifier	Upregulated	High metastasis risk	Predicts recurrence, therapeutic target
MALAT1	lncRNA, PI3K/AKT activator	Upregulated	Poor DFS/OS	Associated with lymph-node spread

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CCAT1	lncRNA, Wnt pathway enhancer	Upregulated	Aggressive phenotype	Target for RNA-based therapy

7. Clinical Applications and Translational Significance

Integration of molecular, immunohistochemical, and epigenetic biomarkers into clinical practice has revolutionized the management of colorectal cancer. **Multiparametric biomarker panels** combining Ki-67, TP53, KRAS/BRAF, MSI, and miRNA expression can more precisely predict recurrence and guide adjuvant therapy (Yoshino et al., 2022).

In the **adjuvant setting**, patients with MSI-H or low TS expression demonstrate improved response to fluoropyrimidine-based regimens, whereas KRAS/BRAF mutations necessitate alternative targeted or immunotherapies. The **liquid biopsy** approach, using circulating tumor DNA (ctDNA) or miRNA profiling, enables real-time monitoring of minimal residual disease and therapy response (Siravegna et al., 2022).

Epigenetic therapies such as **HDAC inhibitors (vorinostat, panobinostat)** and **DNA methyltransferase inhibitors (azacitidine, decitabine)** are being explored in combination with immunotherapy to overcome resistance. The translation of biomarker discoveries into clinical decision-making thus represents a pivotal step toward **personalized oncology**.

8. Discussion

Over the past decades, remarkable progress has been achieved in understanding the molecular pathogenesis and biomarker landscape of colorectal cancer (CRC). The convergence of immunohistochemical, genetic, and epigenetic research has revealed the profound heterogeneity of CRC and identified key molecular determinants of prognosis and therapeutic response. This review synthesized current evidence on proliferation-associated and prognostic biomarkers that collectively shape disease behavior and treatment outcomes.

Proliferation markers such as **Ki-67**, **PCNA**, and **cyclins** remain central to histopathological assessment, serving as accessible surrogates for tumor growth kinetics. Although their prognostic value has varied across studies, methodological standardization has improved their clinical interpretability. Integration with **molecular alterations**—including APC, KRAS, BRAF, TP53, and SMAD4 mutations—has substantially refined risk stratification models. Importantly, **microsatellite instability (MSI)** and **CpG island methylator phenotype (CIMP)** have evolved from descriptive findings to actionable biomarkers guiding immunotherapy and epigenetic interventions.

Recent insights into **non-coding RNAs** and **epigenetic modifications** highlight an additional regulatory dimension of CRC biology. miRNAs such as miR-21 and miR-34a, and lncRNAs including HOTAIR and MALAT1, function as molecular switches that control proliferation, apoptosis, and metastasis. Their detection in plasma and tissue reinforces the feasibility of non-invasive biomarker screening.

Clinically, combining these markers within **multimodal diagnostic algorithms** provides superior prognostic precision compared to single-gene assays. Emerging artificial intelligence–driven pathology platforms are increasingly capable of integrating histopathological and molecular features for real-time risk prediction (Zhang et al., 2023).

Study Limitations and Future Perspectives

Despite substantial advances, several limitations persist. The heterogeneity of biomarker assessment techniques, differing cut-off thresholds, and lack of consensus on interpretation hinder direct comparison between studies. Additionally, many candidate biomarkers remain unvalidated in large prospective cohorts. Future research should emphasize **multi-omics integration**, **longitudinal validation**, and the **clinical utility of composite biomarkers** that combine proliferation indices with genomic and epigenomic data. Establishing

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standardized evaluation pipelines will be critical to implementing precision oncology approaches for CRC globally.

9. Conclusion

Colorectal cancer progression and clinical outcome are tightly governed by complex interactions among proliferative signaling, genetic mutations, and epigenetic alterations. Proliferation-associated proteins (Ki-67, PCNA, cyclins) provide practical pathological insights, while molecular markers (KRAS, BRAF, MSI, CIMP) define biological subtypes with distinct prognostic and therapeutic profiles. The expanding field of non-coding RNAs and methylation patterns further enhances the predictive landscape.

Integration of these biomarkers into clinical workflows supports **personalized treatment**, **optimized surveillance**, and **more accurate prognostication**. Moving forward, large-scale multi-center trials and AI-driven analytical models will accelerate the translation of biomarker research into tangible clinical benefits.

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