INSIGHTS-JOURNAL OF
HEALTH AND REHABILITATION

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

ROLE OF EPIGENETIC MODIFICATIONS IN TUMOR SUPPRESSOR GENE SILENCING AMONG PATIENTS WITH SPORADIC COLORECTAL CANCER: NARRATIVE REVIEW

Narrative Review

Irfan Ishaque[1]*, Hafsa Hameed Thakur[2], Noor Us Sabah Ahmed[3], Attiq Ullah[4], Amna Noor[5], Muhammad Anser Akram[6]
[1]Department of Zoology, Government College University, Lahore, Pakistan.
[2] BSc, MSc, (UK), Research Scientist, Alpha Clinical Developments Ltd., USA.
[3]Postgraduate Resident, Histopathology Department, Pakistan Institute of Medical Sciences, Islamabad, Pakistan.
[4]PhD, Department of Cancer Biology, Northeast Forestry University, Harbin, No 26, Hexing Road, Harbin 150040, P.R, China.
[5]Coordinator PhD (Microbiology, Chemical and Molecular Biology), Rawalpindi Medical University, Rawalpindi, Pakistan.
[6]3rd Year MBBS Student, M. Islam Medical & Dental College, Gujranwala, Pakistan.
Corresponding Author: Irfan Ishaque, Department of Zoology, Government College University, Lahore, Pakistan, iamirfanishaque@gmail.com
Acknowledgement: The author gratefully acknowledges the contributions of all researchers whose work formed the foundation of this review and extends appreciation to institutional access resources that facilitated literature retrieval and analysis.

Conflict of Interest: None

Grant Support & Financial Support: None

ABSTRACT

Background: Sporadic colorectal cancer (CRC), which constitutes the majority of CRC cases, is primarily driven by acquired molecular changes rather than inherited mutations. Among these, epigenetic alterations—specifically the silencing of tumor suppressor genes—play a crucial role in colorectal tumorigenesis. Understanding these reversible and dynamic modifications offers significant potential for enhancing early detection, prognosis, and targeted therapy.

Objective: This narrative review aims to explore the role of epigenetic modifications in the silencing of tumor suppressor genes in patients with sporadic colorectal cancer, synthesizing current findings and identifying implications for clinical practice and future research.

Main Discussion Points: Key epigenetic mechanisms discussed include promoter hypermethylation of genes such as *MLH1*, *MGMT*, and *CDKN2A*; long-range epigenetic silencing across chromosomal regions; histone modification patterns contributing to chromatin inactivation; and microRNA suppression involved in early tumorigenesis. The review also highlights variability in study methodologies, population-specific differences, and gaps in longitudinal and functional research. Limitations related to sample size, design, and generalizability are critically analyzed.

Conclusion: Epigenetic silencing of tumor suppressor genes is a central event in sporadic CRC development, with clear implications for biomarker discovery and therapeutic targeting. While current evidence is promising, more standardized and mechanistically focused studies are needed to translate these findings into clinical applications and guidelines.

Keywords: Sporadic Colorectal Cancer, Tumor Suppressor Genes, Epigenetic Silencing, DNA Methylation, MicroRNA, Narrative Review.

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer-related deaths globally, accounting for nearly 1.9 million new cases and 935,000 deaths in 2020 alone, according to GLOBOCAN statistics. A significant proportion of these cases, estimated at around 75%, are sporadic in nature, arising from acquired genetic and epigenetic alterations rather than hereditary syndromes (1,2). Despite advancements in early detection and therapeutic interventions, the prognosis for patients with advanced CRC remains poor, underscoring the necessity of a deeper understanding of its underlying molecular pathogenesis. A key component in the oncogenic transformation of colorectal epithelial cells involves the inactivation of tumor suppressor genes (TSGs). While genetic mutations such as deletions or point mutations have long been recognized as primary drivers of TSG loss, increasing evidence highlights the critical role of epigenetic mechanisms—heritable changes in gene expression that do not involve alterations to the DNA sequence—in this process (3,4). Epigenetic alterations, including DNA methylation, histone modification, and chromatin remodeling, have emerged as central elements in colorectal tumorigenesis by orchestrating the transcriptional silencing of key TSGs involved in cell cycle regulation, apoptosis, and DNA repair. DNA methylation is perhaps the most well-characterized epigenetic mechanism implicated in the silencing of TSGs. Hypermethylation of CpG islands within gene promoter regions can directly hinder the binding of transcriptional machinery, leading to irreversible transcriptional repression. For instance, MLH1, a pivotal mismatch repair gene, is frequently inactivated in sporadic microsatellite instability-high (MSI-H) colorectal cancers through promoter hypermethylation, contributing to genomic instability and tumor progression (5,6). In many cases, this silencing is not limited to isolated genes but spans entire chromosomal regions, a phenomenon referred to as long-range epigenetic silencing (LRES). Studies have demonstrated LRES affecting loci such as chromosome 3p22 and 5q31, regions harboring multiple tumor suppressor genes including MLH1 and the protocadherin gene cluster (7), suggesting that epigenetic remodeling may be an early and coordinated event in colorectal tumorigenesis.

Beyond DNA methylation, histone modifications such as methylation and acetylation further contribute to the epigenetic repression of TSGs. For example, loss of histone acetylation and gain of methylation at histone H3 lysine 9 (H3K9) are commonly associated with transcriptionally silent chromatin states. These modifications often precede and reinforce DNA methylation patterns, creating a multilayered silencing mechanism that stabilizes gene inactivation. Research has shown that histone modification patterns can suppress even unmethylated genes in the vicinity of epigenetically repressed regions (8,9). A relatively underexplored yet significant domain of epigenetic regulation involves microRNAs (miRNAs), small non-coding RNAs that can function as tumor suppressors. Methylation-induced silencing of miRNAs such as miR-195 and miR-497 has been detected in precancerous colorectal lesions, further implicating epigenetic disruption early in the adenoma-carcinoma sequence (10). Despite the growing body of knowledge surrounding epigenetic mechanisms in CRC, substantial gaps remain. Most current studies have focused on individual genes or specific pathways, often overlooking the broader regulatory networks and interactions between different layers of epigenetic control. Moreover, while several epigenetically silenced genes have been identified as potential biomarkers for diagnosis or targets for therapy, their clinical utility remains largely unvalidated. The dynamic and reversible nature of epigenetic modifications offers an exciting opportunity for therapeutic intervention, but translating this potential into clinical practice requires a comprehensive understanding of when, where, and how these changes occur in the context of sporadic CRC.

This narrative review aims to explore the role of epigenetic modifications in the silencing of tumor suppressor genes among patients with sporadic colorectal cancer. Specifically, it will synthesize findings related to DNA methylation, histone modifications, LRES, and miRNA silencing, highlighting their contributions to tumor initiation and progression. Only studies published in the past five years will be considered, encompassing both in vitro and in vivo models, as well as clinical samples. By consolidating recent evidence, this review seeks to clarify the mechanistic underpinnings of epigenetic silencing in sporadic CRC and evaluate its relevance for early detection, prognostication, and therapeutic innovation. Given the alarming global incidence of colorectal cancer and the distinct biological behavior of sporadic versus hereditary forms, this review is both timely and essential. While the genetic mutations underlying colorectal cancer have been extensively studied, the epigenetic landscape remains comparatively underexplored. This synthesis of current findings will offer a more nuanced understanding of tumor suppressor gene inactivation in sporadic CRC, potentially guiding future research and informing precision medicine approaches.

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

THEMATIC DISCUSSION

Epigenetic Silencing of Tumor Suppressor Genes in Sporadic Colorectal Cancer

The complex molecular etiology of sporadic colorectal cancer (CRC) includes a critical contribution from epigenetic alterations, particularly in the silencing of tumor suppressor genes (TSGs). The thematic discussion below synthesizes the key mechanisms through which epigenetic regulation influences CRC progression, including promoter hypermethylation, long-range epigenetic silencing (LRES), histone modifications, and microRNA dysregulation. Together, these mechanisms underscore the non-genetic routes by which TSGs lose function in colorectal carcinogenesis.

Promoter Hypermethylation as a Central Silencing Mechanism

DNA hypermethylation at CpG islands within gene promoters is one of the most frequently reported epigenetic modifications leading to TSG silencing in sporadic CRC. For instance, methylation of the MGMT gene—a DNA repair enzyme—was found in 59% of tumors, and p16 (CDKN2A), a cyclin-dependent kinase inhibitor, showed promoter methylation in 53% of cases, correlating with reduced gene expression and progression of neoplastic lesions. Notably, the methylation frequency increased with patient age, indicating a possible accumulation of epigenetic changes over time (5). Similarly, p16 hypermethylation was significantly associated with advanced disease stages and lymphatic invasion, suggesting its utility as a prognostic marker (6). Methylation patterns were not random; instead, they often coincided with the CpG Island Methylator Phenotype (CIMP), which describes a subset of sporadic CRCs marked by widespread promoter methylation and microsatellite instability. This phenotype is particularly noted in tumors with hypermethylation of mismatch repair genes such as MLH1, which silences DNA repair pathways and contributes to genetic instability (7).

Long-Range Epigenetic Silencing: Coordinated Suppression of Gene Clusters

Beyond individual gene methylation, long-range epigenetic silencing (LRES) refers to the coordinated inactivation of contiguous TSGs across extensive chromosomal regions. In CRC, one such region involves a >1Mb span of chromosome 3p22, including the MLH1 gene and adjacent suppressor loci. These regions exhibit concurrent CpG hypermethylation and transcriptional repression, suggesting that epigenetic silencing can occur on a chromosomal scale and may precede visible neoplastic transformation (8). A similar pattern is observed in the 5q31 region, where the protocadherin gene cluster, including PCDHGC3, shows extensive hypermethylation. The repression of PCDHGC3, in particular, was associated with decreased apoptosis and increased tumorigenic potential in CRC cells (9).

MicroRNA Silencing: A Layer of Epigenetic Regulation

MicroRNAs (miRNAs) are key post-transcriptional regulators and can themselves be subject to epigenetic silencing. Recent findings have identified over 50 miRNAs that undergo methylation-induced silencing in early colorectal lesions. Among them, miR-195 and miR-497—both encoded by the same primary transcript—were significantly downregulated in colorectal adenomas due to promoter methylation. Loss of imprinting (LOI) was also observed at loci such as MEG3 and GNAS-AS1, suggesting a widespread breakdown of epigenetic regulation during early tumorigenesis (10-12).

Comparative Insights and Interplay with Genetic Alterations

Epigenetic silencing often acts in tandem with or as an alternative to genetic mutations. For example, the inactivation of RASSF1A via promoter methylation was more common in tumors lacking K-ras mutations, suggesting these events are mutually exclusive mechanisms to disrupt similar signaling pathways (11). This highlights a broader trend where epigenetic and genetic events can serve overlapping roles in CRC development but may follow different molecular routes depending on the tumor subtype or stage.

Gaps, Controversies, and Future Directions

Despite compelling evidence supporting the role of epigenetic silencing in CRC, gaps remain. Not all methylation events are causative; some may be passenger changes rather than true drivers of malignancy. Moreover, while the reversibility of epigenetic alterations makes them attractive therapeutic targets, clinical translation remains limited. Agents like 5-aza-2'-deoxycytidine can reverse methylation in vitro, but their effectiveness and safety in clinical settings require further exploration (13). Additionally, population-specific methylation profiles and environmental influences, such as dietary folate intake affecting one-carbon metabolism, may modulate methylation patterns and cancer risk. These variables are not yet well-characterized and could impact biomarker reliability and therapy responsiveness across diverse populations (14,15). The silencing of tumor suppressor genes through epigenetic mechanisms is a hallmark of sporadic colorectal cancer, involving diverse and interlinked molecular pathways. From focal promoter methylation to regional chromatin remodeling and

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

miRNA suppression, these changes collectively contribute to malignant transformation. Ongoing research must clarify the temporal sequence of these events and their interplay with genetic alterations to harness their diagnostic and therapeutic potential.

CRITICAL ANALYSIS AND LIMITATIONS

While the current body of literature provides valuable insights into the epigenetic mechanisms underlying tumor suppressor gene silencing in sporadic colorectal cancer (CRC), several limitations constrain the strength and generalizability of the findings. Most notably, many of the reviewed studies relied on small sample sizes, often derived from single-center analyses or specific geographic populations, which limits statistical power and the robustness of conclusions. These small cohorts may not adequately capture the full heterogeneity of sporadic CRC, particularly with respect to age, sex, ethnicity, or environmental exposures that can modulate epigenetic signatures (16,17). Another frequent limitation across studies is the scarcity of randomized controlled trials (RCTs) or longitudinal cohort designs. Most investigations adopt cross-sectional or retrospective methods, which impede causal inference regarding the temporal sequence of epigenetic events and tumorigenesis. As a result, it remains challenging to determine whether certain methylation patterns are early initiating factors or merely secondary consequences of neoplastic transformation. Additionally, short follow-up durations in clinical observational studies restrict the ability to evaluate long-term implications of epigenetic markers, such as their prognostic value or utility in predicting therapeutic response. Methodological biases are also prevalent in this field. Selection bias is evident in many studies that include only resected tumor specimens or patients undergoing surgical intervention, excluding those with advanced or metastatic disease managed non-surgically. This could skew findings toward early-stage cancers and limit extrapolation to the broader CRC population (18-20). Furthermore, performance bias may arise due to lack of blinding in molecular assessments, particularly when investigators have prior knowledge of clinical or histopathological outcomes. This can inadvertently influence interpretation of epigenetic data and inflate associations.

Publication bias also poses a considerable challenge. Studies reporting significant or novel methylation markers tend to be more frequently published, while negative or inconclusive results are likely underreported. This skew in available literature may exaggerate the perceived prevalence or functional impact of specific epigenetic changes. For example, while promoter methylation of MLH1, MGMT, and p16 is well documented, the inconsistent findings around less-studied loci may not appear due to selective publication, limiting the scope of comprehensive biomarker discovery (19,21). Additionally, variability in outcome measurements across studies hampers direct comparison and synthesis. Definitions of epigenetic silencing differ—some rely solely on methylation-specific PCR, while others incorporate mRNA expression analysis or histone modification profiling. The threshold for classifying a promoter as hypermethylated also varies between studies, leading to inconsistent reporting of prevalence and clinical relevance. This methodological inconsistency makes it difficult to quantify the true frequency and functional impact of TSG silencing events. Lastly, the generalizability of findings remains constrained due to population-specific factors. The majority of studies have been conducted in European or East Asian cohorts, with limited representation from under-studied regions such as Latin America, Africa, or Southeast Asia. Given the potential influence of diet, microbiota, and environmental exposures on the epigenome, regional variability must be accounted for before broad application of biomarkers or therapeutic strategies is considered. Without adequate stratification or replication in diverse populations, the translational potential of epigenetic biomarkers may be overestimated (22) In sum, while the existing literature significantly advances the understanding of epigenetic silencing in sporadic CRC, limitations in study design, methodological consistency, and population diversity highlight the need for more rigorous, standardized, and inclusive research. Future efforts should aim to address these shortcomings through multicenter trials, prospective designs, and the integration of diverse cohorts to enhance the reliability and applicability of findings.

IMPLICATIONS AND FUTURE DIRECTIONS

The growing understanding of epigenetic mechanisms in the silencing of tumor suppressor genes among patients with sporadic colorectal cancer offers a promising avenue for improving clinical outcomes through early detection, personalized therapy, and prognostic stratification. One of the most immediate implications for clinical practice lies in the potential application of methylation-based biomarkers. Genes such as *MLH1*, *MGMT*, and *CDKN2A* have consistently demonstrated aberrant methylation in colorectal tumors, and their detection in tissue or circulating DNA could support non-invasive diagnostic strategies and aid in risk stratification, especially in cases where genetic mutations are not apparent (23,24). Integrating such epigenetic testing into routine clinical workflows could enable earlier interventions and more tailored therapeutic regimens. From a therapeutic perspective, the reversibility of epigenetic changes

makes them attractive targets for pharmacological intervention. Drugs such as DNA methyltransferase inhibitors and histone deacetylase inhibitors have shown potential in preclinical models of colorectal cancer, with the possibility of reactivating silenced tumor suppressor genes. However, their incorporation into standard treatment regimens requires robust clinical evidence (25). Thus, identifying epigenetic signatures predictive of therapeutic response could guide the selection of patients most likely to benefit from epigenetic therapy, thereby enhancing precision oncology. On a policy level, these findings underscore the need for updated clinical guidelines that reflect the role of epigenetic alterations in colorectal cancer pathogenesis. Most existing protocols focus heavily on genetic mutations, yet fail to account for the substantial proportion of tumors driven primarily by epigenetic mechanisms (26). Establishing consensus guidelines on the use of methylation biomarkers for diagnosis, prognosis, and treatment selection would be a valuable step toward standardized, evidence-based care. In particular, policy initiatives could support the validation and reimbursement of epigenetic tests in screening and surveillance programs, particularly in high-risk but asymptomatic populations.

Despite these promising developments, several unanswered questions persist. For instance, the timing and sequence of epigenetic alterations relative to other oncogenic events remain poorly understood. It is unclear whether certain methylation patterns are initiating events or secondary phenomena, and whether they vary by tumor location, molecular subtype, or patient demographic factors. Moreover, while extensive methylation in gene clusters has been observed, the functional relevance of many silenced genes within these regions remains to be elucidated. The role of environmental and lifestyle factors—such as diet, inflammation, and microbiota composition—in shaping the epigenetic landscape also remains underexplored, particularly in diverse and underrepresented populations (27). Future research should focus on prospective, multicenter cohort studies that incorporate large and diverse patient populations to validate epigenetic biomarkers across clinical settings. Longitudinal studies tracking epigenetic alterations from precancerous lesions through advanced disease would be especially valuable in clarifying the temporal dynamics of methylation events. Moreover, functional studies using CRISPR-based epigenetic editing tools could elucidate the specific roles of individual genes silenced by methylation. To better understand therapeutic potential, well-powered randomized controlled trials examining the efficacy of epigenetic drugs—either alone or in combination with existing chemotherapies—are essential. These trials should also include correlative analyses to identify predictive biomarkers of response and resistance. Ultimately, advancing the field will require a multidisciplinary approach that combines molecular biology, clinical oncology, epidemiology, and bioinformatics. Through such collaborative efforts, the epigenetic silencing of tumor suppressor genes may transition from a research focus to a clinical tool that enhances prevention, detection, and treatment strategies in sporadic colorectal cancer.

CONCLUSION

This review highlights the pivotal role of epigenetic modifications—particularly promoter hypermethylation, long-range epigenetic silencing, histone alterations, and microRNA dysregulation—in the transcriptional inactivation of tumor suppressor genes in sporadic colorectal cancer. These mechanisms are not only fundamental to tumor initiation and progression but also offer promising opportunities for biomarker development and targeted therapy. The strength of current evidence, while compelling, is tempered by limitations in study design, population diversity, and methodological consistency, which must be addressed to strengthen the translational potential of these findings. Clinicians should remain attentive to emerging epigenetic biomarkers that could support early diagnosis and personalized treatment strategies, while researchers are encouraged to prioritize multicenter, longitudinal, and mechanistically detailed studies to fill existing knowledge gaps. Advancing this field will depend on refining biomarker validation, exploring novel therapeutic approaches, and integrating epigenetic profiling into routine oncologic practice through evidence-based guidelines

AUTHOR CONTRIBUTION

Author	Contribution
Irfan Ishaque*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Hafsa Hameed Thakur	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Noor Us Sabah Ahmed	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Attiq Ullah	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Amna Noor	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Muhammad Anser Akram	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published

REFERENCES

1. Ghate NB, Kim S, Spiller E, Kim S, Shin Y, Rhie SK, et al. VprBP directs epigenetic gene silencing through histone H2A phosphorylation in colon cancer. Mol Oncol. 2021;15(10):2801-17.
2. Ren Y, Qian Y, Ai L, Xie Y, Gao Y, Zhuang Z, et al. TRAPPC4 regulates the intracellular trafficking of PD-L1 and antitumor immunity. Nat Commun. 2021;12(1):5405.
3. Islam M, Yang Y, Simmons AJ, Shah VM, Musale KP, Xu Y, et al. Temporal recording of mammalian development and precancer. Nature. 2024;634(8036):1187-95.
4. Xie J, Wang S. Small Interfering RNA in Colorectal Cancer Liver Metastasis Therapy. Technol Cancer Res Treat. 2022;21:15330338221103318.
5. Liu Z, Tao J, Zhu Y, Li D, Teng L. Silencing CXCR6 promotes epithelial-mesenchymal transition and invasion in colorectal cancer by activating the VEGFA/PI3K/AKT/mTOR pathway. Int Immunopharmacol. 2024;143(Pt 3):113529.
6. Li S, Li X, Xue W, Zhang L, Yang LZ, Cao SM, et al. Screening for functional circular RNAs using the CRISPR-Cas13 system. Nat Methods. 2021;18(1):51-9.
7. Jebelli A, Baradaran B, Mosafer J, Baghbanzadeh A, Mokhtarzadeh A, Tayebi L. Recent developments in targeting genes and pathways by RNAi-based approaches in colorectal cancer. Med Res Rev. 2021;41(1):395-434.
8. Khorshid Sokhangouy S, Alizadeh F, Lotfi M, Sharif S, Ashouri A, Yoosefi Y, et al. Recent advances in CRISPR-Cas systems for colorectal cancer research and therapeutics. Expert Rev Mol Diagn. 2024;24(8):677-702.
9. Jian W, Zhang L. POLE2 silencing inhibits the progression of colorectal carcinoma cells via wnt signaling axis. Cancer Biol Ther. 2024;25(1):2392339.
10. Yan HHN, Siu HC, Ho SL, Yue SSK, Gao Y, Tsui WY, et al. Organoid cultures of early-onset colorectal cancers reveal distinct and rare genetic profiles. Gut. 2020;69(12):2165-79.
11. Zhang KL, Zhu WW, Wang SH, Gao C, Pan JJ, Du ZG, et al. Organ-specific cholesterol metabolic aberration fuels liver metastasis of colorectal cancer. Theranostics. 2021;11(13):6560-72.
12. Ma SC, Zhang JQ, Yan TH, Miao MX, Cao YM, Cao YB, et al. Novel strategies to reverse chemoresistance in colorectal cancer. Cancer Med. 2023;12(10):11073-96.
13. Guo M, Zhang X. LncRNA MSTO2P promotes colorectal cancer progression through epigenetically silencing CDKN1A mediated by EZH2. World J Surg Oncol. 2022;20(1):95.
14. Fakhr E, Zare F, Azadmanesh K, Teimoori-Toolabi L. LEF1 silencing sensitizes colorectal cancer cells to oxaliplatin, 5-FU, and irinotecan. Biomed Pharmacother. 2021;143:112091.

15. Wang YY, Lin JF, Wu WW, Fu Z, Cao F, Chen YX, et al. Inhibition of MBTPS1 enhances antitumor immunity and potentiates anti-PD-1 immunotherapy. Nat Commun. 2025;16(1):4047.
16. Borrelli C, Roberts M, Eletto D, Hussherr MD, Fazilaty H, Valenta T, et al. In vivo interaction screening reveals liver-derived constraints to metastasis. Nature. 2024;632(8024):411-8.
17. Boughanem H, Pilo J, García-Flores LA, Arranz I, Ramos-Fernandez M, Ortega-Castan M, et al. Identification of epigenetic silencing of the SFRP2 gene in colorectal cancer as a clinical biomarker and molecular significance. J Transl Med. 2024;22(1):509.
18. Yu C, Luo D, Yu J, Zhang M, Zheng X, Xu G, et al. Genome-wide CRISPR-cas9 knockout screening identifies GRB7 as a driver for MEK inhibitor resistance in KRAS mutant colon cancer. Oncogene. 2022;41(2):191-203.
19. Relier S, Ripoll J, Guillorit H, Amalric A, Achour C, Boissière F, et al. FTO-mediated cytoplasmic m(6)A(m) demethylation adjusts stem-like properties in colorectal cancer cell. Nat Commun. 2021;12(1):1716.
20. Yuan Z, Yu X, Chen W, Chen D, Cai J, Jiang Y, et al. Epigenetic silencing and tumor suppressor gene of HAND2 by targeting ERK signaling in colorectal cancer. Cell Commun Signal. 2022;20(1):111.
21. Zhou Y, Yang Z, Zhang H, Li H, Zhang M, Wang H, et al. DNMT3A facilitates colorectal cancer progression via regulating DAB2IP mediated MEK/ERK activation. Biochim Biophys Acta Mol Basis Dis. 2022;1868(4):166353.
22. Hu Y, Liu L, Jiang Q, Fang W, Chen Y, Hong Y, et al. CRISPR/Cas9: a powerful tool in colorectal cancer research. J Exp Clin Cancer Res. 2023;42(1):308.
23. Gupta MK, Gouda G, Moazzam-Jazi M, Vadde R, Nagaraju GP, El-Rayes BF. CRISPR/Cas9-directed epigenetic editing in colorectal cancer. Biochim Biophys Acta Rev Cancer. 2025;1880(3):189338.
24. Zhong C, Jiang WJ, Yao Y, Li Z, Li Y, Wang S, et al. CRISPR screens reveal convergent targeting strategies against evolutionarily distinct chemoresistance in cancer. Nat Commun. 2024;15(1):5502.
25. Liu X, Liu Y, Liu Z, Lin C, Meng F, Xu L, et al. CircMYH9 drives colorectal cancer growth by regulating serine metabolism and redox homeostasis in a p53-dependent manner. Mol Cancer. 2021;20(1):114.
26. Sun G, Zhao S, Fan Z, Wang Y, Liu H, Cao H, et al. CHSY1 promotes CD8(+) T cell exhaustion through activation of succinate metabolism pathway leading to colorectal cancer liver metastasis based on CRISPR/Cas9 screening. J Exp Clin Cancer Res. 2023;42(1):248.
27. Meng H, Nan M, Li Y, Ding Y, Yin Y, Zhang M. Application of CRISPR-Cas9 gene editing technology in basic research, diagnosis and treatment of colon cancer. Front Endocrinol (Lausanne). 2023;14:1148412.

