Article Type: Review
J Name: Modern Phytomorphology
Short name: MP
ISSN: ISSN 2226-3063/eISSN 2227-9555
Year: 2025
Volume: 19
Page numbers: 75-90
DOI: 10.5281/zenodo.200121
(10.5281/zenodo.2025-19)
Short Title: From biomarkers to therapeutics: Exploring long non-coding RNAs in colorectal cancer

REVIEW ARTICLE

From biomarkers to therapeutics: Exploring long non-coding RNAs in colorectal cancer

Mohamed S. Imam[1]*, Randa M. Abdel-Sattar[2], Jawaher A. Ajeebi[3], Mashael Jafari Holal[3], Fahad Mofareh Alosaimi[4], Ayman D. Alshehri[4], Faisal Sultan Alosaimi[4], Sami A. Alshehri[4], Raghad Hamad Alruwaili[5], Taif Abdullah Alayyafi[6], Mohammed Abdullah Alasmari[7], Khalid Manea Alotaibi[8], Rahaf Naif Alhashbari[9], Yasser Mabrouk Bakr[10]

[1] Department of Clinical Pharmacy, National Cancer Institute, Cairo University, Fom El Khalig Square, Kasr Al-Aini Street, Cairo, Egypt
[2] Department of Pharmaceutics, College of Pharmacy, Shaqra University, Shaqra, Saudi Arabia
[3] College of Pharmacy, Jazan University, Jazan, Saudi Arabia
[4] College of Pharmacy, Taif University, Taif, Saudi Arabia
[5] College of Pharmacy, Northern Border University, Rafha, Saudi Arabia
[6] College of Pharmacy, Umm Al-Qura University, Makkah, Saudi Arabia
[7] Al-Nahdi Pharmacies, Riyadh, Saudi Arabia
[8] Al-Dawaa Medical Services Co. Ltd, Riyadh, Saudi Arabia
[9] Ibrand Pharmacy, Taif, Saudi Arabia
[10] Department of Cancer Biology, National Cancer Institute, Cairo University, Fom El Khalig Square, Kasr Al-Aini Street, Cairo, Egypt

***Corresponding author:** Mohamed S. Imam, Department of Clinical Pharmacy, National Cancer Institute, Cairo University, Fom El Khalig Square, Kasr Al-Aini Street, Cairo, Egypt
E-mail: imammohamed311@gmail.com

Received: 02.01.2025, Manuscript No: mp-24-158431 **| Editor Assigned:** 04.01.2025, Pre-QC No. mp-24-158431(PQ) **| Reviewed:** 18.01.2025, QC No. mp-24-158431(Q) **| Revised:** 20.01.2025, Manuscript No. mp-24-158431(R) **| Accepted:** 24.01.2025 **| Published:** 27.01.2025

Abstract

Introduction: Long non-coding RNAs (lncRNAs) have become a cornerstone in the regulation of Colorectal Cancer (CRC) by modulating gene expression, genomic integrity, and DNA Mismatch Repair (MMR) pathways. While many aspects of their functions have been established, the detailed mechanisms by which lncRNAs mediate CRC progression and potential therapeutic targeting remain under intense investigation.
Methods: A comprehensive literature review was conducted, focusing on the latest findings on lncRNAs in CRC. Main discussed topics were transcriptional and post-transcriptional regulation, chromatin dynamics, and signaling pathway interactions. Advanced technologies like CRISPR and RNA-seq and their impacts on lncRNA research were also analyzed.
Results: lncRNAs showed critical roles in CRC through the modulation of transcriptional and epigenetic processes by regulating tumor development and metastasis. Specific lncRNAs, including HOTAIR, CCAT2, and MIR17HG, were pinpointed to play a part in genomic stability maintenance and MMR pathway regulation. It was further stated that lncRNAs hold great potential as biomarkers and therapeutic targets; their role in treatment resistance and immune modulation is one of the most interesting areas under investigation. CRISPR technology and RNA-seq provided new insight into the functional characterization of lncRNAs and their possible clinical application.
Conclusion: lncRNAs are important regulators in colorectal cancer and have provided insights into tumor biology, helping to advance diagnostics and therapies. Their potential as biomarkers and therapeutic targets is further supported by the emerging RNA-based technologies, hence their promise in revolutionizing the management of CRC and improving patient outcomes.

Keywords: Biomarker, Therapeutics, Long non-coding RNA, Colon cancer

Introduction

Colorectal Cancer (CRC) stands as a globally prevalent malignancy, with its mortality primarily attributed to metastasis (Torre et al., 2015; Chen et al., 2016). In China, CRC ranks as the fifth leading cause of cancer-related morbidity and mortality (Chen et al., 2016; Lao et al., 2019). Researchers have diligently explored the intricate pathogenesis of CRC, characterized by the gradual accumulation of genetic and epigenetic alterations within the colonic epithelium. These changes are influenced by environmental factors, ultimately propelling the transformation from normal colonic tissue to colon adenocarcinoma a progression well-documented in the "normal-adenoma-carcinoma-metastasis" sequence (Lao et al., 2019).

Genetic mutations play a pivotal role in CRC susceptibility. Notably, the APC gene has emerged as a central player in Familial Adenomatous Polyposis (FAP), an intriguing model for studying colorectal tumors. With over 1500 pathogenic mutations reported in this gene, it remains a critical focus of investigation (Fokkema et al., 2011; Pezzi et al., 2009). Curiously, up to 20% of individuals with polyposis characteristic of FAP lack a family history of the disease yet still carry germline APC mutations. These mutations predominantly account for FAP cases. Additionally, mutations in the MUTYH gene, involved in base excision repair, have been linked to a recessive form of colorectal polyposis. However, approximately 20% of polyposis patients who undergo genetic testing do not harbor mutations in these genes, leaving them without a definitive genetic diagnosis (Pezzi et al., 2009).

In the Era of Personalized Medicine: Researchers have increasingly recognized the molecular heterogeneity of Colorectal Cancer (CRC), a complex disease with diverse clinical manifestations. Approximately 85% of sporadic CRC cases exhibit chromosomal instability and possess proficient DNA Mismatch Repair (pMMR) mechanisms. In contrast, the remaining 15% of patients harbor defective DNA Mismatch Repair (dMMR) or display high-level Microsatellite Instability (MSI-H) (Boland and Goel., 2010). The MSI-H phenotype is characterized by proximal tumor localization, robust lymphocyte infiltration, elevated histologic tumor grade, and a lower incidence of distant organ metastasis. Interestingly, patients with MSI-H colorectal cancer often experience a more favorable prognosis compared to those with pMMR CRC. Their tumors exhibit unique features, including positive responses to anti-PD-1 immunotherapy. However, these MSI-H tumors do not typically respond to adjuvant chemotherapy based on 5-Fluorouracil (5-FU) (Kloor et al., 2014; Le et al., 2015; Ribic et al., 2003). Despite these intriguing observations, the precise regulation of DNA Mismatch Repair (MMR) in Chinese patients with CRC remains an area of active investigation (Li et al., 2017). Understanding the underlying mechanisms governing MMR dysregulation could provide valuable insights into CRC pathogenesis and potentially guide personalized treatment strategies.

Long noncoding RNAs (lncRNAs) are a group of noncoding RNAs consisting of more than 200 nucleotides that do not encode proteins. These lncRNAs can regulate gene expression at various levels, including epigenetic, transcriptional, and post-transcriptional levels (Liu et al., 2018). In Colorectal Cancer (CRC), the reduced expression of the lncRNA SATB2-AS1 has been found to promote metastasis and influence the tumor microenvironment by regulating SATB2, leading to poor overall survival (Xu et al., 2019). On the other hand, overexpression of the lncRNA UCA1 has been shown to contribute to immune evasion in cancer cells and protect the expression of PDL1 from repression by miRNAs in gastric carcinoma, making it a potential target for immunotherapy (Wang et al., 2019).

Biological functions and mechanisms

lncRNAs in gene expression and genomic stability in Colorectal Cancer (CRC): Long non-coding RNAs (lncRNAs) have emerged as crucial regulators of gene expression and genomic stability in Colorectal Cancer (CRC). Their roles encompass a variety of mechanisms, including transcriptional regulation, post-transcriptional modifications, chromatin remodeling, and involvement in signaling pathways that influence tumor progression and metastasis, as mentioned in tab. 1, illustrated in fig. 1.

Table 1. Key lncRNAs in CRC gene expression and genomic stability.

lncRNA	Mechanism	Target/Pathway	Impact on CRC	Reference
MIR17G	Regulates miR-17-5p	Gene expression modulation	Promotes CRC progression	Xu et al., 2019
HCG18	Sponges miR-1271	Wnt/β-catenin signaling	Enhances CRC cell growth and invasion	Li et al., 2020
CASC2	Regulates cell cycle progression	Tumor suppression	Inhibits CRC cell proliferation	Dai et al., 2019
CCAT2	Associated with chromosomal instability	MYC regulation	Impairs genomic integrity	Ling et al., 2013
FENDRR	Reduces stemness of CRC cells	Impacts therapeutic resistance	Promotes genomic stability	Zhao et al., 2021

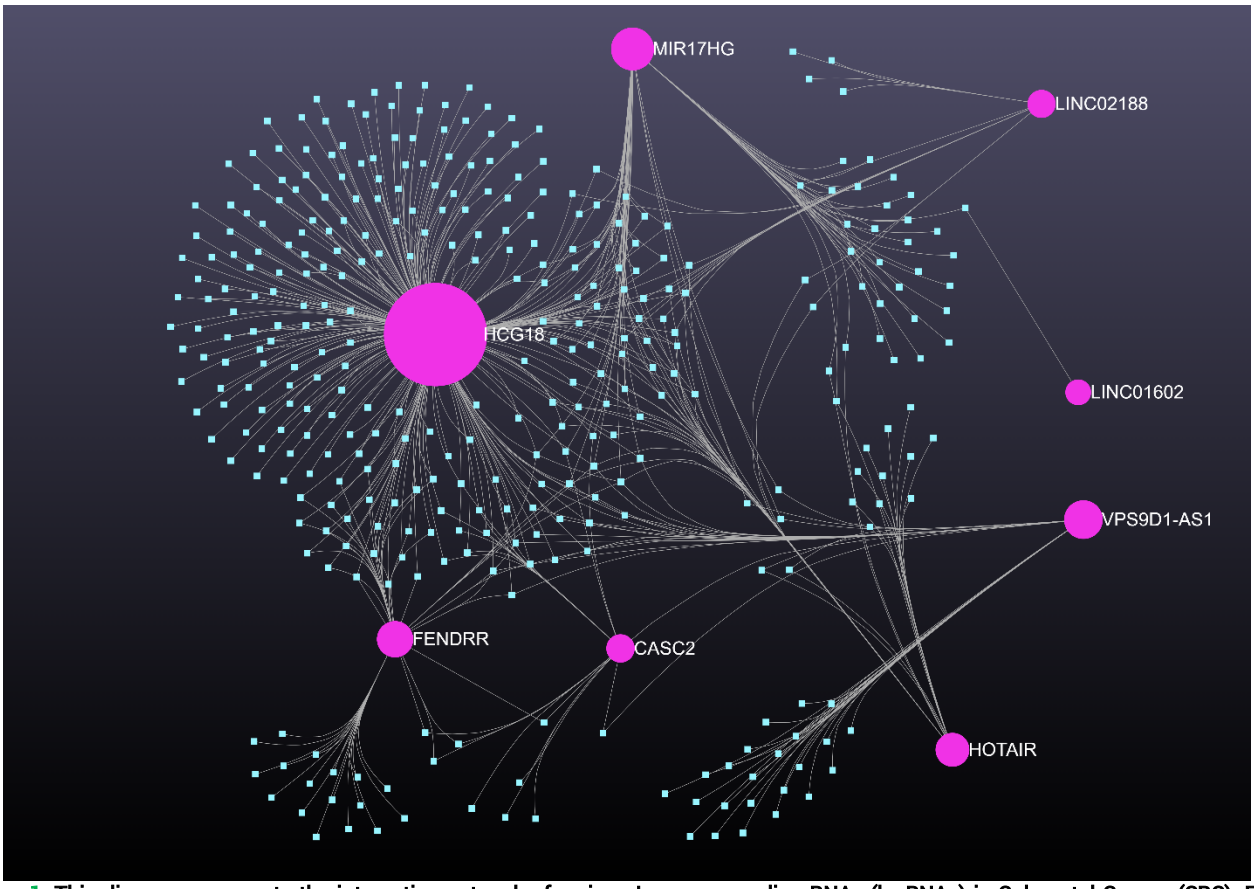

Figure 1. This diagram represents the interaction network of various Long non-coding RNAs (lncRNAs) in Colorectal Cancer (CRC). Each node and connection highlights relationships between lncRNAs and their miRNA, the large central node, HCG18, reflects its extensive network and significant regulatory roles in CRC progression through multiple mechanisms.

One of the primary functions of lncRNAs in CRC is the regulation of gene expression at multiple levels. For instance, lncRNAs can modulate transcription by interacting with transcription factors or chromatin-modifying complexes, thereby influencing the expression of oncogenes and tumor suppressor genes. Xu et al. highlights that lncRNA MIR17HG promotes CRC progression through the regulation of miR-17-5p, demonstrating the intricate interplay between lncRNAs and microRNAs in gene expression modulation (Xu et al., 2019). Similarly, Wei et al. discuss how lncRNAs are involved in transcriptional regulation and chromatin modification, which are critical for maintaining proper gene expression profiles in cancer cells (Wei et al., 2020). Furthermore, Wang et al. emphasize that lncRNAs can serve as biomarkers for prognosis, indicating their potential utility in clinical settings (Wang et al., 2021).

In addition to transcriptional regulation, lncRNAs also play significant roles in post-transcriptional regulation. For example, lncRNA HCG18 has been shown to sponge miR-1271, leading to the upregulation of MTDH and activation of the Wnt/β-catenin signaling pathway, which is pivotal in CRC cell growth and invasion (Li et al., 2020). This mechanism illustrates how lncRNAs can directly influence the stability and availability of microRNAs, thereby affecting downstream

gene expression and cellular behaviors. Moreover, lncRNA CASC2 has been identified as a tumor suppressor that inhibits CRC cell proliferation by regulating cell cycle progression (Dai et al., 2019). Such findings underscore the multifaceted roles of lncRNAs in modulating cellular processes that contribute to tumorigenesis.

Genomic stability is another critical aspect influenced by lncRNAs in CRC. For instance, lncRNA CCAT2 has been implicated in chromosomal instability, a hallmark of many cancers, including CRC. It is associated with the regulation of MYC levels, which is known to affect genomic integrity (Ling et al., 2013). Additionally, lncRNAs like FENDRR have been shown to inhibit the stemness of CRC cells, potentially impacting their ability to maintain genomic stability and resist therapeutic interventions (Zhao et al., 2021). The dysregulation of lncRNAs can lead to aberrant signaling pathways that promote tumor growth and metastasis, highlighting their importance in maintaining genomic stability.

lncRNAs and DNA mismatch repair pathways in CRC: Long non-coding RNAs (lncRNAs) have been increasingly recognized for their roles in modulating DNA Mismatch Repair (MMR) pathways, particularly in the context of Colorectal Cancer (CRC). The MMR system is crucial for maintaining genomic stability by correcting base pair mismatches that occur during DNA replication. Deficiencies in this pathway can lead to Microsatellite Instability (MSI), a characteristic feature of certain CRCs, which is associated with a higher mutation rate and tumorigenesis (Xie et al., 2021; Li et al., 2016).

One significant lncRNA implicated in the regulation of DNA repair mechanisms is HOTAIR. Research indicates that HOTAIR promotes DNA damage repair by targeting key proteins involved in the MMR pathway, such as ATR (Ataxia Telangiectasia and Rad3-related protein) (Hu et al., 2024). This lncRNA has been shown to enhance the cellular response to DNA damage, thereby influencing the efficacy of DNA repair processes. Specifically, HOTAIR's interaction with ATR suggests a mechanism by which lncRNAs can modulate the activity of critical repair proteins, thus affecting the overall efficiency of the MMR system in CRC cells.

Moreover, the expression of certain lncRNAs has been correlated with the status of MMR in CRC. For instance, a study highlighted that six lncRNAs (HOTAIR, BANCR, GK-IT1, LINC01602, CECR7, and LINC02188) are involved in pathways related to DNA replication and mismatch repair, indicating their potential role in CRC metastasis and progression (Li et al., 2020). This suggests that lncRNAs may not only influence the MMR directly but also interact with other cellular pathways that contribute to genomic stability and cancer progression.

The interplay between lncRNAs and the MMR pathway is further underscored by findings that demonstrate how lncRNAs can affect the expression of MMR genes. For example, alterations in lncRNA FAM83H-AS1 and VPS9D1-AS1 expression profiles have been associated with the dysregulation of MMR genes, leading to impaired DNA repair mechanisms and increased susceptibility to genomic instability (Yang et al., 2016). This dysregulation can result in the accumulation of mutations, which is a hallmark of cancer development, particularly in CRC where MMR deficiencies are prevalent (Tab. 2).

Table 2. lncRNAs influencing DNA mismatch repair in CRC.

lncRNA	Role in MMR Pathway	Associated Proteins/Genes	Impact on CRC	Reference
HOTAIR	Promotes DNA damage repair	ATR	Enhances DNA repair efficiency	Hu et al., 2024
BANCR	Involved in MMR-related pathways	DNA replication genes	Linked to CRC metastasis	Li et al., 2020
FAM83H-AS1	Dysregulates MMR genes	Impaired MSH2, MSH6 expression	Contributes to genomic instability	Yang et al., 2016
VPS9D1-AS1	Alters expression of mismatch repair genes	MMR gene downregulation	Drives mutation accumulation	Yang et al., 2016

Pathological relevance

Dysregulated lncRNAs and microsatellite instability in CRC: Dysregulated long non-coding RNAs (lncRNAs) have been implicated in the development of Mismatch Repair (MMR) deficiencies in Colorectal Cancer (CRC), particularly in cases characterized by Microsatellite Instability (MSI). MSI is a consequence of defective MMR pathways, which are critical for correcting DNA replication errors. The presence of MSI is often associated with a higher mutational burden and distinct clinicopathological features, making it a significant focus in CRC research.

One of the mechanisms by which lncRNAs contribute to MMR deficiencies is through the regulation of MMR gene expression. For instance, lncRNAs can modulate the expression of key MMR proteins such as MLH1, MSH2, MSH6, and

PMS2, which are essential for the MMR process (Qu et al., 2022; Mei et al., 2022). Dysregulation of these lncRNAs can lead to the downregulation or silencing of MMR genes, resulting in impaired DNA repair capabilities. This phenomenon is particularly evident in MSI-High (MSI-H) tumors, where epigenetic changes, including promoter hypermethylation of MMR genes, are frequently observed (Sibilio et al., 2022). Such alterations can lead to a loss of function in the MMR system, thereby contributing to the accumulation of mutations characteristic of MSI tumors.

Furthermore, lncRNAs may also influence the MMR pathway through their interactions with various signaling molecules and pathways involved in DNA repair. For example, some lncRNAs have been shown to interact with proteins involved in the DNA damage response, potentially modulating the cellular response to DNA damage and influencing the efficiency of MMR (Qu et al., 2022; Mei et al., 2022). This interaction can create a feedback loop where the dysregulation of lncRNAs exacerbates MMR deficiencies, leading to further genomic instability.

In addition to their regulatory roles, lncRNAs can also be involved in the formation of RNA-DNA hybrids at sites of DNA damage, which can affect the recruitment of repair proteins to these sites (Lu et al., 2018). This mechanism highlights the multifaceted roles of lncRNAs in modulating the MMR process and their potential contribution to the development of MSI in CRC.

The clinical implications of lncRNA dysregulation in MSI CRC are significant. Tumors with MMR deficiencies often exhibit a high mutational burden, which can lead to the generation of neo antigens that make them more susceptible to immunotherapy, particularly immune checkpoint inhibitors (Le et al., 2019; Diaz et al., 2022). Understanding the role of lncRNAs in this context may provide insights into novel therapeutic strategies aimed at targeting these regulatory RNAs to restore MMR function or enhance the efficacy of immunotherapy in MSI CRC patients.

lncRNAs modulating key MMR proteins- MLH1, MSH2, and PMS2: Long non-coding RNAs (lncRNAs) have emerged as crucial regulators in various biological processes, including the modulation of DNA Mismatch Repair (MMR) components such as MLH1, MSH2, and PMS2. Recent studies have identified specific lncRNAs that influence the expression and function of these MMR proteins, thereby impacting genomic stability and cancer progression.

One notable lncRNA is FOXD2-AS1, which has been shown to inhibit the progression of gallbladder cancer by mediating the methylation of MLH1, a key component of the MMR system (Wu et al., 2024). This suggests that FOXD2-AS1 may play a significant role in regulating MLH1 expression, thereby influencing the MMR pathway and its associated functions in DNA repair. Additionally, lncRNA RP11-241J12.3 has been implicated in hepatocellular carcinoma, where it disrupts pyruvate metabolism and the DNA mismatch repair system, further highlighting the connection between lncRNAs and MMR components (Cheng et al., 2022).

Moreover, lncRNA-JADE has been identified as a critical player in linking DNA damage signaling to histone modifications, specifically histone H4 acetylation, which can affect the transcription of MMR genes (Wan et al., 2013). This regulatory mechanism underscores the potential of lncRNAs to modulate not only the expression of MMR components but also their post-translational modifications, which are essential for their functional activity in DNA repair processes.

In the context of specific MMR proteins, MSH2 has been shown to interact with various lncRNAs that regulate its expression and activity. For instance, convergent transcription-induced cell death has been linked to the activation of MSH2, suggesting that lncRNAs may influence MSH2's role in DNA repair and cellular responses to DNA damage (Chatterjee et al., 2016; Lin et al., 2012). Furthermore, the interplay between lncRNAs and MMR components like PMS2 remains an area of active research, with emerging evidence suggesting that lncRNAs can modulate the expression of PMS2 in response to cellular stress and DNA damage (Cheng et al., 2022; Wan et al., 2013).

Overall, the involvement of lncRNAs in the modulation of MMR components such as MLH1, MSH2, and PMS2 highlights their significance in maintaining genomic integrity and their potential as therapeutic targets in cancer treatment. Continued exploration of lncRNA functions in the context of DNA repair mechanisms will provide deeper insights into their roles in cancer biology and therapeutic interventions.

Clinical implications

lncRNA biomarkers for MMR status in CRC: Long non-coding RNAs (lncRNAs) have gained attention as potential biomarkers for Microsatellite Instability (MSI) and Mismatch Repair (MMR) status in Colorectal Cancer (CRC) patients. The expression profiles of lncRNAs can provide insights into the underlying molecular mechanisms of CRC and serve as diagnostic or prognostic indicators.

Several studies have demonstrated that specific lncRNA expression profiles correlate with MSI status in CRC. For instance, a study by Wang et al. identified a panel of six lncRNA pairs that effectively distinguished between Microsatellite-Stable (MSS) and Microsatellite-Instability-High (MSI-H) tumors, achieving approximately 95% accuracy for MSS and 82% for MSI-H CRCs (Wang et al., 2022). This suggests that lncRNA expression profiles can serve as reliable biomarkers for determining MMR status in CRC patients.

Moreover, the relationship between lncRNA expression and the features of MSI in CRC has been further explored. Research has indicated that lncRNAs may be involved in the regulation of genes associated with the MMR pathway, thereby influencing the MSI phenotype (Li et al., 2020). The expression of certain lncRNAs has been linked to the methylation status of MMR genes, such as MLH1, which is a critical factor in the development of MSI (Hughes et al., 2012). This connection implies that lncRNAs not only reflect the MMR status but may also play an active role in the epigenetic regulation of these genes.

Additionally, the presence of MSI in CRC is associated with distinct clinical outcomes and responses to treatment. For instance, tumors exhibiting MSI-H are often more responsive to immunotherapy, making the identification of MSI status crucial for treatment decisions (Hsu et al., 2020; Zhao et al., 2019). The ability of lncRNA profiles to predict MSI status could thus enhance the stratification of CRC patients for targeted therapies, including immune checkpoint inhibitors.

Furthermore, the heterogeneity of CRC, characterized by varying molecular markers and genetic alterations, underscores the potential of lncRNAs as biomarkers. Studies have shown that lncRNA expression patterns differ significantly between MSS and MSI-H tumors, which may reflect the underlying biological differences between these subtypes (Bittoni et al., 2018; Vilar et al., 2010). This variability suggests that lncRNAs could be integrated into existing diagnostic frameworks to improve the accuracy of MSI detection and enhance personalized treatment strategies.

In conclusion, lncRNA expression profiles hold promise as biomarkers for assessing MMR status and MSI in colorectal cancer patients. Their ability to reflect the molecular characteristics of tumors and predict clinical outcomes positions them as valuable tools in the management of CRC.

Targeting lncRNAs to improve MMR and enhance CRC therapies: Targeting long non-coding RNAs (lncRNAs) presents a promising strategy for restoring Mismatch Repair (MMR) functionality and enhancing therapeutic efficacy in Colorectal Cancer (CRC) treatment. The dysregulation of lncRNAs has been implicated in various aspects of cancer biology, including tumor progression, metastasis, and resistance to chemotherapy, making them attractive targets for therapeutic intervention.

One of the key mechanisms by which lncRNAs influence CRC is through their role as competing endogenous RNAs (ceRNAs). For instance, lncRNA CRNDE has been shown to promote CRC cell proliferation and metastasis by sponging microRNA-136, thereby preventing it from downregulating its target genes (Gao et al., 2021). This ceRNA mechanism highlights the potential of targeting lncRNAs to modulate miRNA activity and restore the expression of tumor suppressor genes, which could enhance MMR functionality and improve treatment responses.

Additionally, lncRNAs such as TP53TG1 have demonstrated tumor-suppressive activities in CRC. Studies indicate that TP53TG1 can increase sensitivity to DNA-damaging agents like 5-fluorouracil and oxaliplatin, suggesting that restoring or enhancing the expression of this lncRNA could improve the efficacy of conventional chemotherapy (Masoumi et al., 2021). This approach could be particularly beneficial for patients with MMR-deficient tumors, where traditional therapies often show limited effectiveness.

Moreover, the targeting of specific lncRNAs has been proposed as a therapeutic strategy to overcome drug resistance in CRC. For example, lncRNA UCA1 has been implicated in 5-fluorouracil resistance, and its downregulation has been

associated with enhanced sensitivity to this chemotherapeutic agent (Bian et al., 2016). By inhibiting lncRNAs that contribute to drug resistance, it may be possible to restore the effectiveness of existing treatments and improve patient outcomes.

The development of novel therapeutic modalities, such as Antisense Oligonucleotides (ASOs) and RNA interference (RNAi), provides tools for specifically targeting lncRNAs in CRC. These strategies have shown promise in preclinical models, where they effectively reduced the expression of oncogenic lncRNAs and inhibited tumor growth. For instance, the knockdown of lncRNA DLEU1 has been associated with reduced proliferation and migration of CRC cells, indicating that targeting this lncRNA could hinder tumor progression (Liu et al., 2018).

Furthermore, the integration of lncRNA expression profiles into clinical practice could aid in the stratification of CRC patients for personalized therapies. By identifying lncRNAs associated with MMR status or treatment response, clinicians could tailor therapeutic approaches to individual patients, potentially improving efficacy and reducing adverse effects (Wu et al., 2023).

In summary, targeting lncRNAs holds significant potential for restoring MMR functionality and enhancing therapeutic efficacy in colorectal cancer treatment. By modulating the expression and activity of lncRNAs, it may be possible to improve the effectiveness of existing therapies, overcome drug resistance, and provide personalized treatment options for CRC patients.

Interactions and crosstalk

lncRNAs, microRNAs, and non-coding RNA networks in MMR regulation: The interplay between long non-coding RNAs (lncRNAs), microRNAs (miRNAs), and other non-coding RNAs is crucial in regulating Mismatch Repair (MMR) mechanisms, particularly in the context of Colorectal Cancer (CRC). This relationship underscores the complexity of gene regulation and the potential for these non-coding RNAs to serve as therapeutic targets or biomarkers in cancer treatment.

LncRNAs have been shown to interact with miRNAs, functioning as competing endogenous RNAs (ceRNAs). This interaction can modulate the availability of miRNAs to their target mRNAs, thereby influencing gene expression related to MMR. For instance, lncRNA MALAT1 has been implicated in various cancers, including CRC, where it regulates downstream miRNAs that affect cell proliferation and migration (Huang et al., 2021). By sequestering specific miRNAs, lncRNAs can prevent these miRNAs from repressing their target genes, which may include those involved in the MMR pathway.

Moreover, lncRNAs can directly influence the expression of MMR genes. For example, lncRNA LINP1 has been shown to promote the repair of DNA double-strand breaks by interacting with key proteins involved in the Non-Homologous End Joining (NHEJ) pathway (Zhang et al., 2016). This suggests that lncRNAs not only serve as regulatory molecules but also play active roles in the DNA Damage Response (DDR) by facilitating the repair processes that are critical for maintaining genomic stability.

The relationship between lncRNAs and miRNAs extends to the regulation of signaling pathways that are essential for MMR. For instance, lncRNA-DDSR1 has been shown to enhance Homologous Recombination (HR) repair through its interaction with BRCA1 and other repair proteins, which is regulated by the ATM-NF-κB signaling pathway (Xie et al., 2019). This highlights how lncRNAs can integrate signals from various pathways to modulate the cellular response to DNA damage.

In addition to lncRNAs and miRNAs, other non-coding RNAs, such as Circular RNAs (circRNAs), also play significant roles in regulating MMR mechanisms. CircRNAs can act as sponges for miRNAs, similarly to lncRNAs, thereby influencing the expression of MMR-related genes (Gu et al., 2023). This adds another layer of complexity to the regulatory networks involving non-coding RNAs in CRC.

In conclusion, the relationship between lncRNAs, miRNAs, and other non-coding RNAs is integral to the regulation of MMR mechanisms in colorectal cancer. Their interactions and regulatory functions highlight the potential for these non-coding RNAs to serve as biomarkers for MMR status and as therapeutic targets to enhance the efficacy of cancer treatments.

lncRNAs and the tumor microenvironment in MMR-deficient CRC: Long non-coding RNAs (lncRNAs) play a pivotal role in the interaction between tumor cells and the Tumor Microenvironment (TME), significantly influencing

Colorectal Cancer (CRC) progression, particularly in the context of Mismatch Repair (MMR) deficiencies. The TME consists of various cell types, including immune cells, fibroblasts, and endothelial cells, as well as extracellular matrix components, all of which can be modulated by lncRNAs as illustrated in fig. 2.

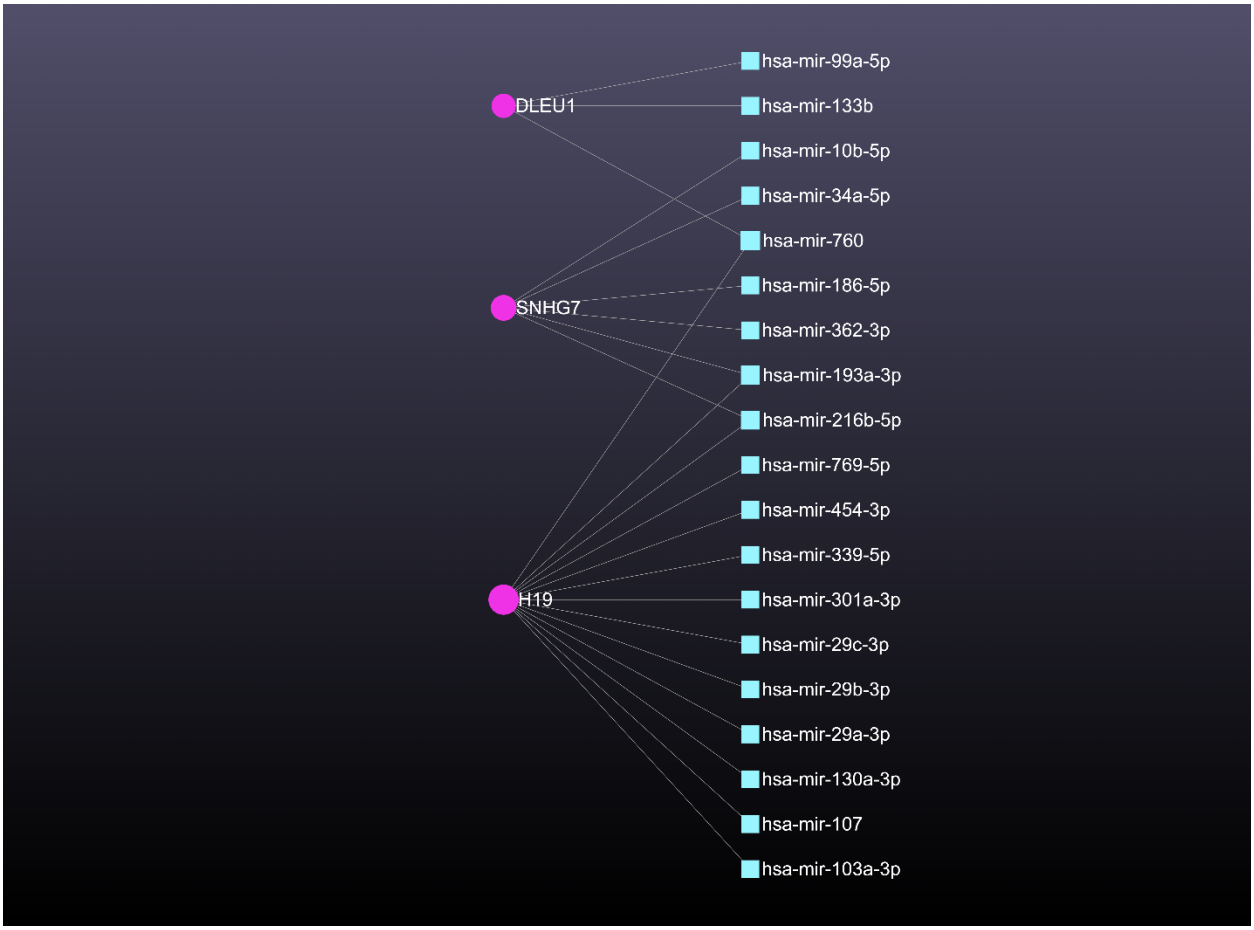

Figure 2. This diagram showcases the interaction network between long non-coding RNAs (lncRNAs) and specific microRNAs (miRNAs), highlighting the regulatory relationships crucial in cancer progression, particularly colorectal cancer (CRC).

One of the mechanisms through which lncRNAs influence the TME is by regulating immune cell infiltration and activity. For instance, lncRNA NKILA has been shown to modulate T cell apoptosis, enhancing the cytotoxic activity of T cells within the TME (Zhou et al., 2022). This regulatory effect can be particularly important in MMR-deficient CRC, where the immune response may be altered due to the accumulation of mutations and the resulting neoantigens. By promoting T cell survival and function, lncRNAs can potentially enhance the anti-tumor immune response, making them attractive targets for immunotherapy.

Moreover, lncRNAs can affect the angiogenic properties of the TME. For example, lncRNA H19 has been implicated in the modulation of endothelial behavior through exosome-mediated communication, promoting angiogenesis in liver cancer (Conigliaro et al., 2015). This suggests that lncRNAs can influence the vascularization of tumors, which is critical for tumor growth and metastasis. In CRC, the ability of lncRNAs to regulate angiogenesis could have significant implications for tumor progression, particularly in the context of MMR deficiencies, where the tumor microenvironment may become more permissive to growth and spread.

Another important aspect is the role of lncRNAs in metabolic reprogramming within the TME. LncRNA LINRIS, for instance, has been shown to stabilize IGF2BP2 and promote aerobic glycolysis in CRC cells (Wang et al., 2019). This metabolic shift can create a more favorable environment for tumor growth and survival, particularly in MMR-deficient tumors that may already exhibit altered metabolic pathways due to their genetic instability.

Additionally, lncRNAs can interact with other non-coding RNAs, such as miRNAs, to modulate the TME. For example, lncRNA SNHG7 has been reported to sponge miR-216b, leading to increased expression of GALNT1, which promotes CRC cell proliferation and liver metastasis (Shan et al., 2018). This interaction not only highlights the regulatory complexity involving lncRNAs and miRNAs but also underscores the potential for lncRNAs to influence the TME through their effects on miRNA activity.

Furthermore, lncRNAs can also affect the expression of key proteins involved in MMR. For instance, lncRNA DLEU1 has been shown to contribute to CRC progression by activating KPNA3, which may indirectly influence MMR pathways and the tumor's response to DNA damage. This connection suggests that lncRNAs may play a dual role in modulating both the TME and the intrinsic properties of tumor cells, including their MMR capabilities.

In summary, lncRNAs interact with the tumor microenvironment in multiple ways, influencing immune cell dynamics, angiogenesis, metabolic reprogramming, and the expression of MMR-related proteins. These interactions are particularly relevant in the context of MMR deficiencies in CRC, as they can significantly impact tumor progression and therapeutic responses. Targeting lncRNAs may offer novel strategies for enhancing the efficacy of existing treatments and improving patient outcomes in CRC.

Therapeutic opportunities in targeting lncRNAs for CRC with MMR deficiencies

The development of lncRNA-targeted therapies for Colorectal Cancer (CRC) with Mismatch Repair (MMR) deficiencies presents both significant challenges and promising opportunities. Understanding these dynamics is crucial for advancing therapeutic strategies that can improve patient outcomes.

Challenges in therapeutic development

Heterogeneity of MMR deficiencies: MMR-deficient tumors harbor different genetic changes, making the search for common lncRNA targets difficult. In addition, variability in the expression of MMR proteins, such as MLH1, MSH2, and PMS2, adds complexity to therapeutic approaches (McCarthy et al., 2019; Rajarajan et al., 2020).

Complexity of regulatory networks: LncRNAs can bind to microRNAs (miRNAs) and other non-coding RNAs, leading to highly complex regulatory networks. Hence, targeting a specific lncRNA in isolation may not consider its broader interactions with the potential for unintended effects (Liu et al., 2018).

Delivery mechanisms: The effective administration of lncRNA-targeted treatments remains a big challenge because of the large size and low stability inherent in lncRNAs. Innovative delivery mechanisms are being investigated, such as nanoparticles and exosomes; however, these technologies require refinement (He et al., 2020).

Resistance mechanisms: CRC cells can develop resistance to therapies, including those targeting lncRNAs. For example, lncRNA UCA1 has been shown to be involved in resistance to 5-fluorouracil. Overcoming such resistance mechanisms is critical for effective treatment.

Opportunities for therapeutic advancements

Biomarker development: LncRNAs have been promising candidates as biomarkers for MMR status and responses to CRC treatment. For instance, certain lncRNA expression patterns are correlated with MSI status, which could help stratify patients for better treatment decisions (Zhao et al., 2019; Yang et al., 2018). Incorporating lncRNA biomarkers into clinical diagnostics can improve the potential for early detection and prognosis.

Combination therapies: Combining lncRNA-targeted approaches with existing treatments, such as Immune Checkpoint Inhibitors (ICIs) or chemotherapy, may improve therapeutic outcomes. MMR-deficient tumors, especially MSI-H subtypes, show an encouraging response to ICIs like pembrolizumab. Targeting the lncRNAs in charge of immune evasion and drug resistance might further enhance these responses (McCarthy et al., 2019; Siraj et al., 2021).

Exosome-based delivery: Exosome-mediated delivery of lncRNAs is a new approach in enhancing specificity while reducing off-target effects. They can carry therapeutic lncRNAs, thus stabilizing them and improving the efficiency of their delivery in vivo (He et al., 2020).

Research and development: The growing body of research on lncRNAs in CRC provides a rich foundation for developing targeted therapies. Studies have identified various lncRNAs that play roles in CRC progression and MMR deficiencies, such as lncRNA PVT1 and its involvement in tumorigenesis (Wu et al., 2020). Continued exploration of these lncRNAs could lead to the identification of novel therapeutic targets.

Influence of lncRNAs on the efficacy of current CRC treatments: Immune checkpoint inhibitors and chemotherapy

Long non-coding RNAs (lncRNAs) have emerged as significant regulators in the response of Colorectal Cancer (CRC) to existing treatments, including immune Checkpoint Inhibitors (ICIs) and chemotherapy. Their influence on treatment efficacy is multifaceted, involving modulation of immune responses, tumor microenvironment dynamics, and interactions with other non-coding RNAs.

Influence on immune checkpoint inhibitors

Immune microenvironment modulation: LncRNAs can significantly impact the immune microenvironment of CRC, which is crucial for the effectiveness of ICIs. For instance, lncRNAs associated with immune cell infiltration can determine whether a tumor is classified as "immune-hot" or "immune-cold" (Huang et al., 2022). Immune-hot tumors, characterized by high levels of immune cell infiltration, are more likely to respond favorably to ICIs. Conversely, immune-cold tumors may exhibit resistance due to a lack of pre-existing anti-tumor immune responses. Targeting lncRNAs that influence immune cell dynamics could enhance the efficacy of ICIs by converting immune-cold tumors into immune-hot ones.

Regulation of immune checkpoint expression: Some lncRNAs have been shown to regulate the expression of immune checkpoints such as PD-1 and CTLA-4. For example, lncRNA signatures that correlate with immune checkpoint expression may predict responses to ICIs (Shi et al., 2017). By modulating the expression of these checkpoints, lncRNAs can influence the effectiveness of therapies designed to block these pathways, potentially enhancing anti-tumor immune responses (Oliveira et al., 2019).

Combination therapies: The integration of lncRNA-targeted therapies with ICIs presents an opportunity to improve treatment outcomes. For instance, combining ICIs with agents that target specific lncRNAs associated with immune evasion could restore immune reactivity and enhance tumor cell killing. This approach could be particularly beneficial in CRC patients with MMR deficiencies, who often exhibit high levels of Microsatellite Instability (MSI-H) and may respond better to ICIs (Zhong et al., 2023).

Influence on chemotherapy

Modulation of drug resistance: LncRNAs have been implicated in the development of resistance to chemotherapy in CRC. For example, lncRNA UCA1 has been associated with 5-fluorouracil resistance, suggesting that targeting this lncRNA could sensitize tumors to chemotherapy (Zhong et al., 2023). By understanding the role of lncRNAs in drug resistance mechanisms, it may be possible to develop combination therapies that enhance the efficacy of existing chemotherapeutic agents.

Impact on tumor metabolism: LncRNAs can also influence metabolic pathways within tumors, affecting their response to chemotherapy. For instance, lncRNA signatures related to glycolysis have been shown to correlate with treatment outcomes in CRC (Zhong et al., 2023). By targeting lncRNAs that regulate metabolic pathways, it may be possible to enhance the sensitivity of CRC cells to chemotherapy, particularly in MMR-deficient tumors that may exhibit altered metabolic profiles.

Predictive biomarkers: The expression levels of specific lncRNAs may serve as predictive biomarkers for chemotherapy response. Identifying lncRNA signatures associated with treatment outcomes could help stratify patients for more personalized treatment approaches, allowing for the selection of therapies that are more likely to be effective based on the tumor's lncRNA profile (Chen et al., 2023; Mahoney et al., 2015).

Emerging technologies and research directions

Technological advances in lncRNA research- CRISPR and RNA-seq: Recent advancements in technologies such as CRISPR and RNA sequencing (RNA-seq) have significantly enhanced our understanding of long non-coding RNAs (lncRNAs) and their functions in Colorectal Cancer (CRC). These technologies provide powerful tools for investigating the roles of lncRNAs in cancer biology, particularly in the context of CRC.

CRISPR technologies

CRISPR/Cas13d for RNA targeting: The development of CRISPR/Cas13d technology has enabled researchers to specifically target and knock down lncRNAs with high efficiency. This RNA-targeting system allows for the precise depletion of lncRNAs, facilitating the study of their functional roles in CRC (Zhang et al., 2021). By utilizing this technology, researchers can investigate the impact of lncRNAs on tumor growth, metastasis, and treatment responses.

High-throughput screening: CRISPR-based high-throughput screening methods have emerged as a powerful approach for identifying lncRNAs that function as oncogenes or tumor suppressors. These screens can systematically evaluate the effects of lncRNA knockouts on cancer cell behavior, providing insights into their roles in CRC progression (Esposito et al., 2019; Lucere et al., 2020). This capability is particularly valuable for uncovering novel therapeutic targets among the vast array of lncRNAs.

Functional characterization: CRISPR/Cas9 technology has been adapted for the functional characterization of lncRNAs by enabling the manipulation of their expression levels. This allows researchers to explore the biological functions of specific lncRNAs in CRC, including their interactions with other non-coding RNAs and their influence on gene expression (Hazan et al., 2021). Such studies can reveal the complex regulatory networks involving lncRNAs in CRC.

RNA sequencing (RNA-seq)

Comprehensive transcriptome analysis: RNA-seq has revolutionized the study of lncRNAs by providing a comprehensive view of the transcriptome. This technology allows for the identification and quantification of lncRNAs in CRC samples, facilitating the discovery of novel lncRNAs associated with tumorigenesis and progression (Zheng et al., 2019; Yamada et al., 2018). The ability to analyze the entire transcriptome enhances our understanding of lncRNA expression patterns and their potential as biomarkers.

Benchmarking and standardization: Recent studies have focused on benchmarking lncRNA quantification methods in RNA-seq, ensuring reliable and reproducible results. This is crucial for accurately assessing lncRNA expression levels in cancer samples, which can inform the development of lncRNA-based diagnostic and therapeutic strategies (Zheng et al., 2019). Improved methodologies enhance the robustness of findings related to lncRNAs in CRC.

Integration with other omics data: RNA-seq data can be integrated with other omics data, such as genomics and epigenomics, to provide a more comprehensive understanding of lncRNA functions. This integrative approach can reveal how lncRNAs interact with genomic and epigenetic factors to influence CRC biology (Gao et al., 2021). Such insights are essential for elucidating the mechanisms by which lncRNAs contribute to cancer development and progression.

Opportunities for future research

The advancements in CRISPR and RNA-seq technologies present numerous opportunities for future research on lncRNAs in CRC:

Targeted therapeutics: The ability to manipulate lncRNA expression using CRISPR technologies opens avenues for developing targeted therapies that could inhibit oncogenic lncRNAs or restore the function of tumor-suppressive lncRNAs (Esposito et al., 2019; Lucere et al., 2020. This could lead to novel treatment strategies for CRC patients.

Biomarker discovery: RNA-seq can facilitate the identification of lncRNAs that serve as biomarkers for CRC diagnosis, prognosis, or treatment response. The integration of lncRNA profiles with clinical data could enhance personalized medicine approaches in CRC (Zheng et al., 2019; Yamada et al., 2018).

Understanding mechanisms of action: Continued research utilizing these technologies will deepen our understanding of the molecular mechanisms by which lncRNAs influence CRC. This includes their roles in regulating gene expression, interacting with miRNAs, and modulating the tumor microenvironment (Zhang et al., 2018; Xiang et al., 2022).

Bridging knowledge gaps in lncRNA-MMR interactions in CRC

Understanding the connection between Long non-coding RNAs (lncRNAs) and Mismatch Repair (MMR) mechanisms in Colorectal Cancer (CRC) is crucial for developing targeted therapies and improving patient outcomes. However, several key knowledge gaps and future research priorities remain in this area.

Key knowledge gaps

Functional characterization of LncRNAs: While numerous lncRNAs have been identified in CRC, their specific roles in regulating MMR pathways are not fully understood. For instance, lncRNAs like ZNFX1-AS1 and DANCR have been implicated in CRC progression, but their direct involvement in MMR mechanisms remains to be elucidated (Shi et al., 2019; Wang et al., 2018). Comprehensive functional studies are needed to clarify how these lncRNAs interact with MMR proteins and influence DNA repair processes.

Mechanistic insights: The precise molecular mechanisms by which lncRNAs regulate MMR are still unclear. For example, while some lncRNAs have been shown to act as competing endogenous RNAs (ceRNAs) for miRNAs, the downstream effects of these interactions on MMR gene expression and activity need further investigation (Shi et al., 2019; Wang et al., 2018). Understanding these mechanisms will be essential for identifying potential therapeutic targets.

Tissue and context-specific roles: LncRNAs may exhibit tissue-specific expression patterns and functions. For instance, lncRNA ZNFX1-AS1 has been reported to have different roles in various cancers, indicating that its function in CRC may differ from its role in other malignancies (Shi et al., 2019). Future research should focus on characterizing the context-dependent roles of lncRNAs in CRC, particularly in relation to MMR status.

Integration with other regulatory networks: LncRNAs do not operate in isolation; they are part of complex regulatory networks involving other non-coding RNAs, transcription factors, and signaling pathways. The interplay between lncRNAs and these factors in the context of MMR deficiencies is not well understood. Investigating these interactions could provide insights into the broader regulatory landscape of CRC (Wang et al., 2021).

Clinical relevance and biomarker development: Although some lncRNAs have shown promise as biomarkers for CRC prognosis, their specific association with MMR status and treatment response needs to be established. For example, while lncRNA u50535 has been linked to CRC growth and metastasis, its correlation with MMR status and potential as a therapeutic target requires further validation (Yu et al., 2018). Research should prioritize the identification of lncRNA biomarkers that can predict MMR status and guide treatment decisions.

Future research priorities

High-throughput screening: Utilizing CRISPR and RNA-seq technologies for high-throughput screening of lncRNAs in CRC could accelerate the identification of novel lncRNAs involved in MMR pathways. These approaches can help elucidate the functional roles of lncRNAs and their interactions with MMR proteins (Zhang et al., 2021).

Mechanistic studies: Future studies should focus on dissecting the molecular mechanisms by which lncRNAs influence MMR. This includes investigating their interactions with MMR proteins, their effects on gene expression, and their roles in modulating the tumor microenvironment (Shi et al., 2019; Wang et al., 2018).

Therapeutic targeting: Research should explore the potential of targeting specific lncRNAs to restore MMR functionality in CRC. This could involve developing lncRNA inhibitors or utilizing RNA-based therapies to modulate lncRNA expression (Esposito et al., 2019). Preclinical studies are needed to assess the efficacy of these approaches in MMR-deficient CRC models.

Clinical trials: Conducting clinical trials to evaluate the efficacy of lncRNA-targeted therapies in CRC patients, particularly those with MMR deficiencies, will be essential for translating research findings into clinical practice. These

trials should also assess the potential of lncRNAs as biomarkers for predicting treatment responses (Siraj et al., 2021; Wang et al., 2021).

Integration of omics data: Integrating lncRNA expression profiles with genomic, transcriptomic, and proteomic data could provide a comprehensive understanding of their roles in CRC. This system's biology approach may reveal novel insights into the interplay between lncRNAs and MMR mechanisms, facilitating the identification of new therapeutic targets (Gao et al., 2021; Zhang et al., 2018).

Conclusions

Long non-coding RNAs (lncRNAs) have come to be recognized as playing important roles in Colorectal Cancer (CRC) through the regulation of gene expression, genomic stability, and DNA Mismatch Repair (MMR) pathways, thus being promising biomarkers and therapeutic targets. Their interactions with signaling networks, microRNAs, and the tumor microenvironment underline even more their complexity and clinical relevance, especially in MMR-deficient CRC. Despite challenges in delivery mechanisms and regulatory intricacies, advancements in technologies such as CRISPR and RNA-seq have opened up new opportunities for targeted therapies and precision medicine. Future mechanistic insight-driven and clinically validating research will be instrumental in tapping the full potential of lncRNAs for improving CRC diagnosis, treatment, and patient outcomes.

Author Contributions

Conceptualization, Y.M.B., M.S.I., and R.M.A.; methodology, formal analysis, investigation, resources, data curation, writing original draft preparation, writing review and editing Y.M.B., M.S.I., R.M.A., F.M.A., A.D.A., R.H.A., F.S.A., J.A.A., M.J.H, S.A.A., M.A.A., K.M.A., R.N.A. and T.A.A.; visualization, Y.M.B., and M.S.I.; supervision, Y.M.B., and M.S.I.; project administration, M.S.I. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest

The authors declare no conflicts of interest.

References

Bian Z, Jin L, Zhang J, Yin Y, Quan C, Hu Y, Feng Y, Liu H, Fei B, Mao Y, Zhou L (2016). LncRNA—UCA1 enhances cell proliferation and 5-fluorouracil resistance in colorectal cancer by inhibiting miR-204-5p. *Sci. Rep.* **6**:1-2.

Bittoni A, Sotte V, Meletani T, Cantini L, Giampieri R, Berardi R (2018). Immunotherapy in colorectal cancer treatment: actual landscape and future perspectives. *J. Cancer. Metastasis. Treat.* Oct 26;**4:**55.

Boland CR, Goel A. (2010). Microsatellite instability in colorectal cancer. Gastroenterology. **138:**2073-2087.

Chatterjee N, Lin Y, Wilson JH (2016). Mismatch repair enhances convergent transcription-induced cell death at trinucleotide repeats by activating ATR. *DNA repair.* **42**:26-32.

Chen R, Wei JM (2023). Integrated analysis identifies oxidative stress-related lncRNAs associated with progression and prognosis in colorectal cancer. *BMC bioinform.* **24**:76.

Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F. (2016). Cancer statistics in China, 2015. *CA Cancer J Clin.* **66:**115-132.

Cheng L, Hu S, Ma J, Shu Y, Chen Y, Zhang B, Qi Z, Wang Y, Zhang Y, Zhang Y, Cheng P (2022). Long noncoding RNA RP11-241J12. 3 targeting pyruvate carboxylase promotes hepatocellular carcinoma aggressiveness by disrupting pyruvate metabolism and the DNA mismatch repair system. *Mol. Biomed.* **3**:4.

Conigliaro A, Costa V, Lo Dico A, Saieva L, Buccheri S, Dieli F, Manno M, Raccosta S, Mancone C, Tripodi M, De Leo G (2015). CD90+ liver cancer cells modulate endothelial cell phenotype through the release of exosomes containing H19 lncRNA. *Mol. cancer.* **14**:1-1.

Dai W, Mu L, Guo S, Yan K, Tian C, Zhang S. (2019). Berberine promotes apoptosis of colorectal cancer via regulation of the long non-coding RNA (LncRNA) cancer susceptibility candidate 2 (CASC2)/AU-binding factor 1 (AUF1)/B-cell cll/ lymphoma 2 (Bcl-2) axis. *Med Sci Monit*. **25:**730-738.

Diaz LA, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, Smith D, Garcia-Carbonero R, Benavides M, Gibbs P, de la Fourchardiere C (2022). Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study. *Lancet Oncol*. **23**:659-670.

Esposito R, Bosch N, Lanzós A, Polidori T, Pulido-Quetglas C, Johnson R (2019). Hacking the cancer genome: profiling therapeutically actionable long non-coding RNAs using CRISPR-Cas9 screening. Cancer cell. **35**:545-557.

Fokkema IFAC, Taschner PEM, Schaafsma GCP, Celli J, Laros JFJ, den Dunnen JT. (2011). LOVD v.2.0: The next generation in gene variant databases. Hum Mutat. **32:**557-563.

Gao Y, Shang S, Guo S, Li X, Zhou H, Liu H, Sun Y, Wang J, Wang P, Zhi H, Li X (2021). Lnc2Cancer 3.0: an updated resource for experimentally supported lncRNA/circRNA cancer associations and web tools based on RNA-seq and scRNA-seq data. *Nucleic Acids Res*. **49**:1251-1258.

Gu Y, Zhao H, Zheng L, Zhou C, Han Y, Wu A, Jia Z, Xia T, Zhi Q (2023). Non-coding RNAs and colitis-associated cancer: Mechanisms and clinical applications. *Clin. Transl. Med*. **13**:1253.

Hazan J, Bester AC (2021). CRISPR-based approaches for the high-throughput characterization of long non-coding RNAs. *Non-coding RNA*. **7**:79.

He Q, Long J, Yin Y, Li Y, Lei X, Li Z, Zhu W (2020). Emerging roles of lncRNAs in the formation and progression of colorectal cancer. *Front. oncol*. **9**:1542.

Hu H, Wang W, Ji C, Tian Q, He Y, Liu N. (2024). LncRNA HOTAIR promotes DNA damage repair and radioresistance by targeting ATR in colorectal cancer. *Oncol Res*. **32**:1335-1346.

Huang E, Ma T, Zhou J, Ma N, Yang W, Liu C, Hou Z, Chen S, Zong Z, Zeng B, Li Y (2022). A novel senescence-associated LncRNA signature predicts the prognosis and tumor microenvironment of patients with colorectal cancer: A bioinformatics analysis. *J. Gastrointest. Oncol*. **13**:1842.

Huang J, Wang FH, Wang L, Li Y, Lu J, Chen J (2021). LncRNA MALAT1 promotes proliferation and migration of airway smooth muscle cells in asthma by downregulating microRNA-216a. *Saudi J. Biol. Sci*. **28**:4124-4131.

Hughes LA, Khalid-de Bakker CA, Smits KM, van den Brandt PA, Jonkers D, Ahuja N, Herman JG, Weijenberg MP, van Engeland M (2012). The CpG island methylator phenotype in colorectal cancer: progress and problems. *Biochim. Biophys. Acta (BBA)-Rev. Cancer*. **1825**:77-85.

Kloor M, Staffa L, Ahadova A, von Knebel Doeberitz M. (2014). Clinical significance of microsatellite instability in colorectal cancer. *Langenbecks Arch Surg*. **399:**23-31.

Lao Y, Li Q, Zhou Q, Ye X, Liu Y, Lu Y. (2019). Long noncoding RNA ENST00000455974 plays an oncogenic role through up-regulating JAG2 in human DNA mismatch repair-proficient colon cancer. *Biochem. Biophys. Res. Commun*. **508:**339-347.

Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK. (2019). Phase II Open-Label Study of Pembrolizumab in Treatment-Refractory, Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: KEYNOTE-164. *J Clin Oncol*. **38:**11-19.

Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD. (2015). PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med*. **372:**2509-2520.

Li Q, Meng X, Zhang Y, Zhao Y, Zheng Y, Li Y. (2017). Variable Levels of Long Noncoding RNA Expression in DNA Mismatch Repair-Proficient Early-Stage Colon Cancer. *Dig Dis Sci*. **62:**1235-1245.

Li S, Lin X, Zhang X, Zheng X, Ye H, Wang S. (2020). A Robust 6-lncRNA Prognostic Signature for Predicting the Prognosis of Patients With Colorectal Cancer Metastasis. *Front Med (Lausanne)*. **7:**604987.

Li S, Wu T, Zhang D, Sun X, Zhang X. (2020). The long non-coding RNA HCG18 promotes the growth and invasion of colorectal cancer cells through sponging miR-1271 and upregulating MTDH/Wnt/β-catenin. *Clin Exp Pharmacol Physiol*. **47:**703-712.

Li Z, Pearlman AH, Hsieh P. (2016). DNA mismatch repair and the DNA damage response. *DNA Repair (Amst)*. **38:**94-101.

Lin Y, Wilson JH. Nucleotide excision repair, mismatch repair, and R-loops modulate convergent transcription-induced cell death and repeat instability. *PLoS. ONE*. **7**:46807.

Ling H, Spizzo R, Atlasi Y, Nicoloso M, Shimizu M, Redis RS. (2013). CCAT2, a novel noncoding RNA mapping to 8q24, underlies metastatic progression and chromosomal instability in colon cancer. *Genome Res*. **23:**1446-1461.

Liu T, Han Z, Li H, Zhu Y, Sun Z, Zhu A (2018). LncRNA DLEU1 contributes to colorectal cancer progression via activation of KPNA3. *Mol. cancer*. **17**:1-3.

Liu Z, Long X, Chen K, Zhu J, Yang F. (2018). Comprehensive Analysis of Long Noncoding RNAs and Messenger RNAs Expression Profiles in Patients with Marjolin Ulcer. *Med Sci Monit*. **24:**7828-7240.

Lu WT, Hawley BR, Skalka GL, Baldock RA, Smith EM, Bader AS. (2018). Drosha drives the formation of DNA:RNA hybrids around DNA break sites to facilitate DNA repair. *Nat Commun*. **9:**532.

Lucere KM, O'Malley MM, Diermeier SD (2020). Functional screening techniques to identify long non-coding RNAs as therapeutic targets in cancer. *Cancers*. **12**:3695.

Mahoney KM, Rennert PD, Freeman GJ (2015). Combination cancer immunotherapy and new immunomodulatory targets. *Nat. Rev. Drug Discov*. **14**:561-584.

Masoumi F, Saraiva SM, Bouzo BL, López-López R, Esteller M, Diaz-Lagares A, de la Fuente M (2021). Modulation of colorectal tumor behavior via lncrna tp53tg1-lipidic nanosystem. *Pharmaceutics*. **13**:1507.

McCarthy AJ, Capo-Chichi JM, Spence T, Grenier S, Stockley T, Kamel-Reid S, Serra S, Sabatini P, Chetty R (2019). Heterogenous loss of Mismatch Repair (MMR) protein expression: a challenge for immunohistochemical interpretation and microsatellite instability (MSI) evaluation. *J. Pathol. Clin. Res*. **5**:115-129.

Mei WJ, Wu ZH, Li Y, Song B, Wang RY, Zhang LF. (2022). Clinicopathological characteristics of high microsatellite instability/mismatch repair-deficient colorectal cancer: A narrative review. *Front Immunol*. **13:**1019582.

Oliveira AF, Bretes L, Furtado I (2019). Review of PD-1/PD-L1 inhibitors in metastatic dMMR/MSI-H colorectal cancer. *Front. Oncol*. **9**:396.

Pezzi A, Tricarico R, Pironi D, Marini M, Curia MC. (2009). Relative role of APC and MUTYH mutations in the pathogenesis of familial adenomatous polyposis. Scand J Gastroenterol. **44:**1092-1100.

Qu H, Chen L, Liu M, Li Y, Zhang X, Zhang C. (2022). Long-Read Nanopore Sequencing Identifies Mismatch Repair-Deficient Related Genes with Alternative Splicing in Colorectal Cancer. *Dis Markers*. **2022:**8450953.

Rajarajan S, Jose B, Correa M, Sengupta S, Prabhu JS (2020). Identification of colorectal cancers with defective DNA damage repair by immunohistochemical profiling of mismatch repair proteins, CDX2 and BRCA1. *Mol. Clin. Oncol*. **13**:1.

Ribic CM, Sargent DJ, Moore MJ, Thibodeau SN, French AJ, Goldberg RM. (2003). Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N Engl J Med*. **349:**247-257.

Roudko V, Cimen Bozkus C, Greenbaum B, Lucas A, Samstein R, Bhardwaj N (2021). Lynch syndrome and MSI-H cancers: from mechanisms to "off-the-shelf" cancer vaccines. *Front. Immunol*. **12**:757804.

Shan Y, Ma J, Pan Y, Hu J, Liu B, Jia L (2018). LncRNA SNHG7 sponges miR-216b to promote proliferation and liver metastasis of colorectal cancer through upregulating GALNT1. *Cell. Death. Dis*. **9**:722.

Shi L, Hong X, Ba L, He X, Xiong Y, Ding Q, Yang S, Peng G (2019). Long non-coding RNA ZNFX1-AS1 promotes the tumor progression and metastasis of colorectal cancer by acting as a competing endogenous RNA of miR-144 to regulate EZH2 expression. *Cell. death. dis*. **10**:150.

Shi Y, Zou Z, Kerr D (2017). Why Don't Immune Checkpoint Inhibitors Work in Colorectal Cancer. *J. Gastrointest. Cancer. Stromal. Tumor*. **2**:2.

Sibilio P, Belardinilli F, Licursi V, Paci P, Giannini G. (2022). An integrative in-silico analysis discloses a novel molecular subset of colorectal cancer possibly eligible for immune checkpoint immunotherapy. Biol Direct. **17**:10.

Siraj AK, Parvathareddy SK, Annaiyappanaidu P, Haqawi W, Al-Rasheed M, AlManea HM, AlHussaini HF, Al-Dayel F, Al-Kuraya KS (2021). PD-L1 expression is associated with deficient mismatch repair and poor prognosis in middle eastern colorectal cancers. *J. Pers. Med*. **11**:73.

Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. (2015). Global cancer statistics, 2012. *CA Cancer J Clin*. **65**:87-108.

Vilar E, Gruber SB (2010). Microsatellite instability in colorectal cancer—the stable evidence. *Nat. Rev. Clin. Oncol*. **7**:153-162.

Wan G, Hu X, Liu Y, Han C, Sood AK, Calin GA, Zhang X, Lu X (2013). A novel non-coding RNA lncRNA-JADE connects DNA damage signalling to histone H4 acetylation. *EMBO J*. **32**:2833-2847.

Wang CJ, Zhu CC, Xu J, Wang M, Zhao W, Liu Q. (2019). The lncRNA UCA1 promotes proliferation, migration, immune escape and inhibits apoptosis in gastric cancer by sponging anti-tumor miRNAs. *Mol Cancer*. **18:**115.

Wang N, Song X, Zhang Y, Zhang J, Xue N, Li Y. (2021). Knockdown of lncRNA CCAT1 Inhibits the Progression of Colorectal Cancer via hsa-miR-4679 Mediating the Downregulation of GNG10. *J Immunol Res*. **2021:**6675861.

Wang O, Shi D, Li Y, Zhou X, Yan H, Yao Q (2022). lncRNA pair as candidate diagnostic signature for colorectal cancer based on the within-sample relative expression levels. *Front. Oncol*. **12**:912882.

Wang X, Qiu W, Liu H, Li T, Ye H, Li Y, Xu X, Chen P (2021). The prognostic value of combining CD133 and mismatch repair proteins in patients with colorectal cancer. *Clin. Exp. Pharmacol. Physiol*. **48**:54-63.

Wang Y, Lu JH, Wu QN, Jin Y, Wang DS, Chen YX, Liu J, Luo XJ, Meng Q, Pu HY, Wang YN (2019). LncRNA LINRIS stabilizes IGF2BP2 and promotes the aerobic glycolysis in colorectal cancer. *Mol. cancer*. **18**:1-8.

Wang Y, Lu Z, Wang N, Feng J, Zhang J, Luan L, Zhao W, Zeng X (2018). Long noncoding RNA DANCR promotes colorectal cancer proliferation and metastasis via miR-577 sponging. *Exp. mol. med*. **50**:1-7.

Wei J, Ge X, Tang Y, Qian Y, Bai W, Zhang W. (2020). An autophagy-related long noncoding RNA signature contributes to poor prognosis in colorectal cancer. *J Oncol*. **2020:**4728945.

Wu H, Wei M, Jiang X, Tan J, Xu W, Fan X, Zhang R, Ding C, Zhao F, Shao X, Zhang Z (2020). lncRNA PVT1 promotes tumorigenesis of colorectal cancer by stabilizing miR-16-5p and interacting with the VEGFA/VEGFR1/AKT axis. *Mol. Ther. Nucleic. Acids*. **20**:438-450.

Wu J, Yu J, Zhu H, Chen Z, Liang Y, Chen Q, Li G, Wan Y (2024). LncRNA HOXB-AS3 promotes proliferation, migration, and invasion of gallbladder cancer cells by activating the MEK/ERK pathway. *Heliyon*. **10**:35906.

Wu Y, Xu X (2023). Long non-coding RNA signature in colorectal cancer: research progression and clinical application. *Cancer. Cell. Int*. **23**:28.

Xiang J, Gao L, Jing HY, Liu YX, Wang HF, Chang ZW, Liu SH, Yu L, Wang GY (2022). Construction of CeRNA regulatory network based on WGCNA reveals diagnosis biomarkers for colorectal cancer. *BMC cancer*. **22**:991.

Xie L, Huang R, Liu S, Wu W, Su A, Li R, Liu X, Lei Y, Sun H, Liu X, Xu S (2019). A positive feedback loop of SIRT1 and miR17HG promotes the repair of DNA double-stranded breaks. *Cell Cycle*. **18**:2110-2123.

Xie T, Gao M, Li L, Tan J, Yuan F, Lv Y. (2021). Heterogeneous constitutional mismatch repair deficiency with MSH6 missense mutation clinically benefits from pembrolizumab and regorafenib combination therapy: a case report and literature review. *Hered Cancer Clin Pract*. **19:**6.

Xu J, Ji L, Liang Y, Wan Z, Zheng W, Song X. (2019). Long noncoding RNA MIR17HG promotes colorectal cancer progression via miR-17-5p. *Cancer Res*. **79:**4882-4895.

Xu M, Chen X, Lin K, Zeng K, Liu X, Pan B. (2019). LncRNA SATB2-AS1 inhibits tumor metastasis and affects the tumor immune cell microenvironment in colorectal cancer by regulating SATB2. *Mol Cancer*. **18:**135.

Yamada A, Yu P, Lin W, Okugawa Y, Boland CR, Goel A (2018). A RNA-Sequencing approach for the identification of novel long non-coding RNA biomarkers in colorectal cancer. *Sci. Rep*. **8**:575.

Yang L, Xu L, Wang Q, Wang M, An G. (2016). Dysregulation of long non-coding RNA profiles in human colorectal cancer and its association with overall survival. Oncol Lett. **12:**4068-4074.

Yang YN, Zhang R, Du JW, Yuan HH, Li YJ, Wei XL, Du XX, Jiang SL, Han Y (2018). Predictive role of UCA1-containing exosomes in cetuximab-resistant colorectal cancer. *Cancer. Cell. Int*. **18**:1-1.

Yu X, Yuan Z, Yang Z, Chen D, Kim T, Cui Y, Luo Q, Liu Z, Yang Z, Fan X, Chen D (2018). The novel long noncoding RNA u50535 promotes colorectal cancer growth and metastasis by regulating CCL20. *Cell death dis*. **9**:751.

Zhang M, Weng W, Zhang Q, Wu Y, Ni S, Tan C, Xu M, Sun H, Liu C, Wei P, Du X (2018). The lncRNA NEAT1 activates Wnt/β-catenin signaling and promotes colorectal cancer progression via interacting with DDX5. *J. Hematol. Oncol*. **11**:1-3.

Zhang Y, He Q, Hu Z, Feng Y, Fan L, Tang Z, Yuan J, Shan W, Li C, Hu X, Tanyi JL (2016). Long noncoding RNA LINP1 regulates repair of DNA double-strand breaks in triple-negative breast cancer. *Nat. Struct. Mol. Biol*. **23**:522-530.

Zhang Y, Nguyen TM, Zhang XO, Wang L, Phan T, Clohessy JG, Pandolfi PP (2021). Optimized RNA-targeting CRISPR/Cas13d technology outperforms shRNA in identifying functional circRNAs. *Genome biol*. **22**:1-22.

Zhao P, Li L, Jiang X, Li Q (2019). Mismatch repair deficiency/microsatellite instability-high as a predictor for anti-PD-1/PD-L1 immunotherapy efficacy. *J. Hematol. Oncol*. **12**:1-4.

Zhao X, Wu J, Li Y, Ye F, Wang C. (2021). Long non-coding RNA FENDRR inhibits the stemness of colorectal cancer cells through directly binding to Sox2 RNA. *Bioengineered*. **12:**8698-8708.

Zheng H, Brennan K, Hernaez M, Gevaert O (2019). Benchmark of long non-coding RNA quantification for RNA sequencing of cancer samples. *Gigascience*. **8**:145.

Zhong X, He X, Wang Y, Hu Z, Huang H, Zhao S, Zhang H, Wei P, Li D (2023). Construction of a prognostic glycolysis-related lncRNA signature for patients with colorectal cancer. *Cancer Med*. **12**:930-948.

Zhou X, Aikemu B, Li S, Shao Y, Jia H, Huang L, Hong H, Zhang S, Tang Q, Pan R, Sun J (2022). Comprehensive exploration of tumor immune microenvironment feature and therapeutic response in colorectal cancer based on a novel immune-related long non-coding RNA prognostic signature. *Front. Genet*. **13**:962575.