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REVIEW

Non-Coding RNAs and cernas: emerging modulators of drug response in colorectal cancer

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Abstract
Colorectal cancer (CRC) is still one of the most common cancers and a leading cause of cancer morbidity worldwide. A significant issue that should be paid much attention to is its resistance to anticancer agents. Non-coding RNAs (ncRNAs), such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), have been identified as important regulators of drug response and drug resistance in CRC. In this review, we provide a comprehensive assessment of the studies conducted in the field of investigating the role of ncRNAs in drug resistance to prominent anticancer agents used in CRC, including 5-fluorouracil (5-FU), oxaliplatin, cetuximab, bevacizumab, and regorafenib. We focussed specifically on the miRNAs, lncRNAs, and circRNAs associated with resistance to each drug individually, even within the context of combination therapies, such as FOLFOX. We also reviewed competing endogenous RNA (ceRNAs) networks and their relationship with drug sensitivity and resistance and new therapeutic strategies to manage drug resistance in CRC and also analyzed the role of ceRNA networks in modulating drug response and its implications for new approaches to overcome drug resistance in CRC. This article also discusses findings from human clinical trials, highlighting evidence from patient studies that validate the role of targeting ceRNA and ncRNA networks in improving drug sensitivity, overcoming resistance, and enhancing therapeutic outcomes in CRC. It supports the targeting of ncRNA and ceRNA networks as potential therapies to improve treatment outcomes and drug resistance in CRC.

Keywords CeRNA network · Drug resistance · Colorectal cancer

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Abbreviations

CRC	Colorectal cancer
ncRNAs	Non-coding RNAs
miRNAs	MicroRNAs
lncRNAs	Long non-coding RNAs ()
circRNAs	Circular RNAs
5-FU	5-fluorouracil
ceRNAs	Competing endogenous RNA
mCRC	Metastatic CRC
MoAb	Monoclonal antibody
MSI-H	Microsatellite instability-high
dMMR	Deficient mismatch repair
OS	Overall survival
sncRNAs	Small non-coding RNAs
siRNAs	Small interfering RNAs
piRNAs	Piwi-interacting RNAs
OXA	Oxaliplatin
DEGs	Differentially expressed genes
CTX	Cetuximab

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PFS Progression-free survival

Introduction

Colorectal cancer (CRC) ranks third in global incidence (9.6%) and second in mortality (9.3%), according to GLOBOCAN 2022. By 2040, the number of cases is projected to rise by 63%, reaching 3.2 million annually, while deaths are expected to increase by 73%, totaling 1.6 million. This alarming trend underscores the urgent need for enhanced prevention and treatment strategies [1]. The severity of the disease and the available treatment options are determined by stage [2, 3]. While surgery is the standard treatment for stages 0–II CRC, stage II is at high risk and stage III CRC requires both surgery and adjuvant chemotherapy. For stage IV and recurrent CRC, the treatment involves surgery, cytotoxic agents, targeted therapy, and immunotherapy. Unfortunately, there is still no established cure for these advanced stages [2]. Since the 1950 s, chemotherapy based on 5-fluorouracil (5-FU) has been the cornerstone of treatment for CRC patients [4]. At the beginning of the new century, other cytotoxic drugs such as oxaliplatin, irinotecan, and capecitabine, the oral pro-drug of 5-FU have been introduced. Standard treatment for first-line metastatic CRC (mCRC) typically involves combining 5-FU and leucovorin with either oxaliplatin or irinotecan associated with a monoclonal antibody (MoAb) (i.e., anti-EGFR or anti-VEGF MoAbs) [5, 6]. The immune checkpoint inhibitors nivolumab and ipilimumab, anti-PD1 and anti-CTLA4 MoAbs, respectively, are used alone (nivolumab) or in combination (nivolumab and ipilimumab) in mCRC patients who progressed following first-line treatment, in the presence of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors. Regorafenib, an antiangiogenic protein kinase inhibitor, is also administered in mCRC patients who progressed after first-line treatment. Drug resistance to anticancer agents presents a significant challenge for the growing number of CRC patients. In recent decades, the overall survival (OS) rate for individuals with advanced colon cancer has improved due to new pharmacological regimens. However, despite the increased response rates CRC becomes resistant to all the available drugs, independently from their typologies. Thus drug resistance limits the effectiveness of anticancer drugs and ultimately represents the main cause of treatment failure [7].

Recent advancements in transcriptomics have underscored the significance of non-coding RNAs (ncRNAs), in human cancer. NcRNAs are RNA molecules transcribed from the genome's non-coding regions. They are categorized into small non-coding RNAs (sncRNAs) and long non-coding RNAs (lncRNAs). SncRNAs are less than 200 nucleotides long and include microRNAs (miRNAs), small interfering RNAs (siRNAs), piwi-interacting RNAs (piRNAs), and small nucleolar RNAs (snoRNAs). LncRNAs are over 200 nucleotides long and include circular RNAs (circRNAs) [8]. Notably, lncRNAs and circRNAs can critically modulate chemoresistance by acting as competitive endogenous RNAs (ceRNAs). These ceRNAs sequester tumor-suppressive miRNAs, thereby derepressing key downstream genes involved in apoptosis, epithelial-mesenchymal transition (EMT), and autophagy [9].The ceRNA hypothesis thus provides a powerful mechanistic framework for understanding how these RNA interactions fine-tune gene expression networks to promote survival in drug-resistant CRC cells [10, 11]. Experimental evidence indicates that the dysregulation of specific ncRNAs may play a role in tumor initiation, progression, metastasis, and the development of resistance to therapy [12, 13]. On the other side, ceRNAs regulate each other post-transcriptionally by competing for shared miRNAs, linking the functions of protein-coding mRNAs and ncRNAs (miRNAs, lncRNAs, pseudogenic RNAs, and circRNAs). Any transcript with miRNA response elements can act as a ceRNA, representing a significant form of gene regulation. CeRNA activity is influenced by factors like abundance, subcellular localization, miRNA binding affinity, RNA editing, secondary structures, and RNA-binding proteins. Disruptions in these factors can deregulate ceRNA networks, potentially leading to diseases like cancer [14].

As a result, ncRNAs could serve not only as predictive and prognostic biomarkers for CRC [15] but also as targets for new ncRNA-based therapeutic strategies aimed at overcoming drug resistance [16, 17]. This review aims to investigate the role of ncRNAs and their related ceRNA networks in drug resistance as a biomarker and prognostic factor in CRC (Figs. 1, 2 and 3).

MiRNAs regulate drug resistance in CRC

miRNAs have 19–24 nucleotides and the genomic loci encoding miRNAs (miR loci) are often located within non-coding intronic regions of the transcriptome [18]. miRNAs only participate in the regulation of gene expression at the post-transcriptional level and do not encode any proteins. In humans, the number of miRNA genes is significantly lower than previously reported. Curated databases such as miRBase and MirGeneDB list approximately 500 to 600 miRNA genes and about 2,300 mature miRNAs. These sncRNAs regulate a substantial proportion of protein-coding genes, thereby influencing a wide range of biological processes and disease pathways [19]. Targeting miRNAs presents a robust strategy for modulating the cellular pathways they influence, thereby paving the way for innovative and effective

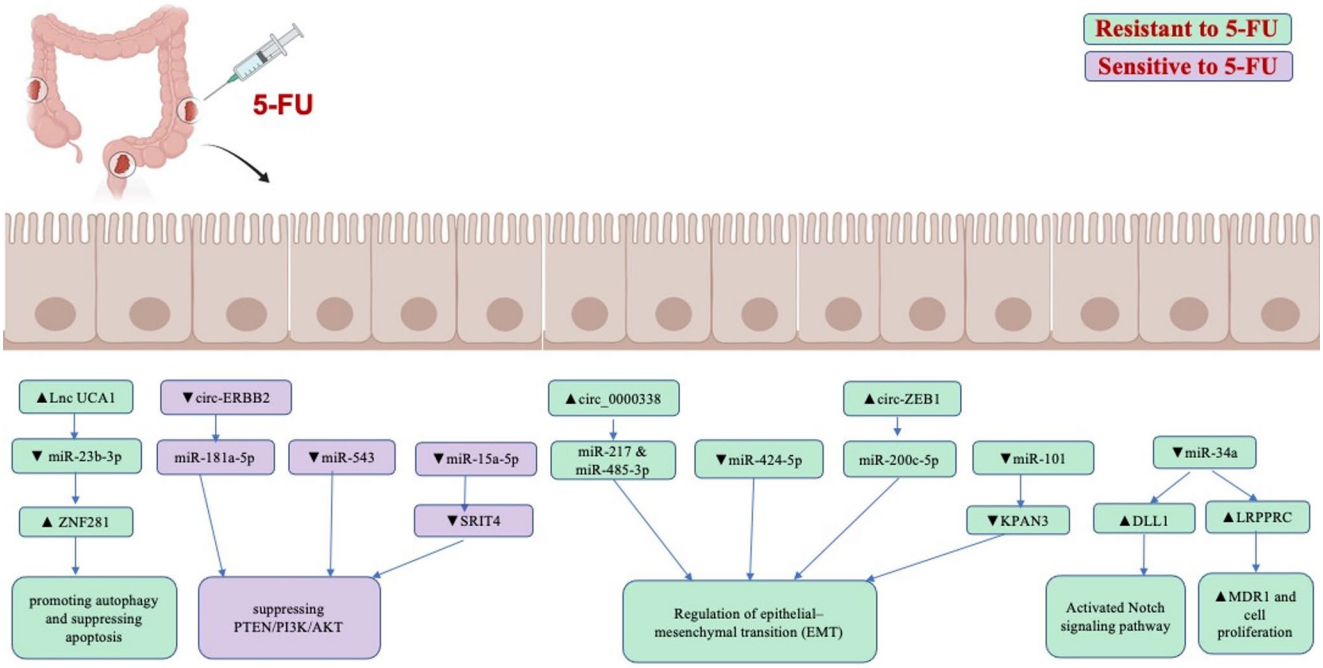

Fig. 1 Non-coding RNAs and pathways involved in CRC resistance to 5-FU

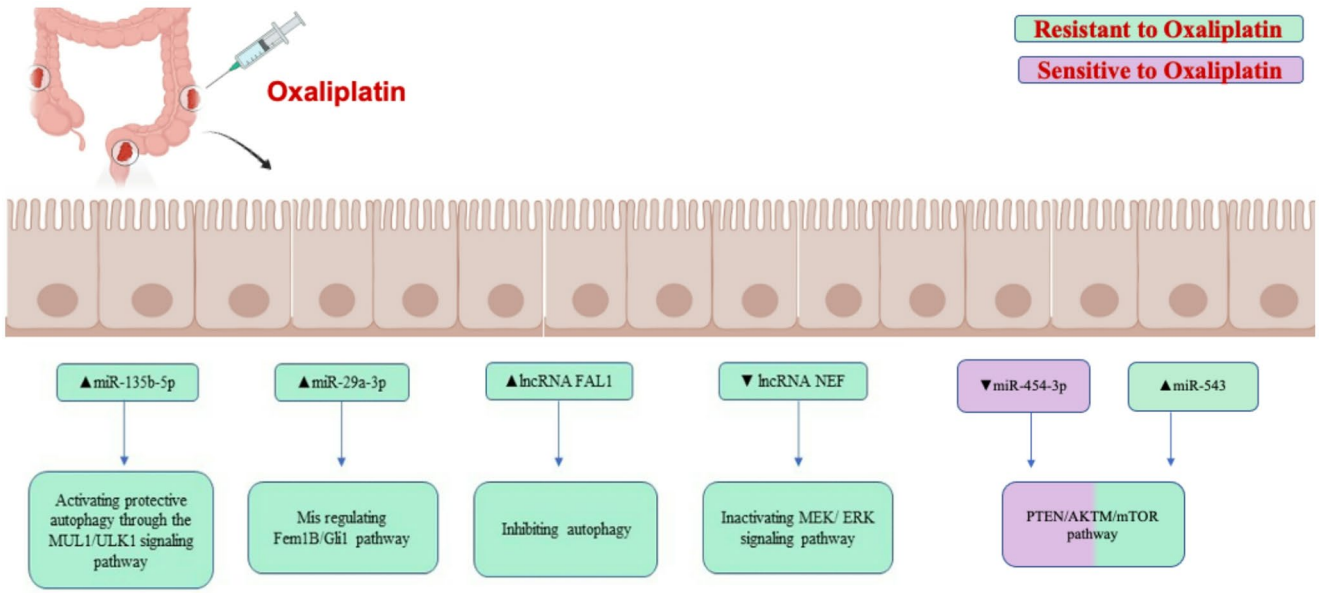

Fig. 2 Non-coding RNAs and pathways involved in CRC resistance to oxaliplatin

cancer therapies; These strategies include pharmacological and genetic interventions. Therefore, miRNAs can modulate drug sensitivity and resistance in various cancers such as CRC [20]. A set of miRNAs regulating the response of CRC to chemotherapeutic drugs has been identified. miRNAs that target genes associated with drug resistance may increase the sensitivity of CRC to chemotherapy, whereas miRNAs that target genes that diminish drug resistance could enhance drug resistance in CRC. Table 1 summarizes miRNAs and their targets involved in the drug resistance of CRC.

MiRNAs related to 5-FU resistance

5-FU-based protocols represent the standard treatment of CRC patients and frequently yield response rates exceeding 50%. Non-responder patients develop 5-FU-resistant tumors [21]. The number of miRNAs potentially involved

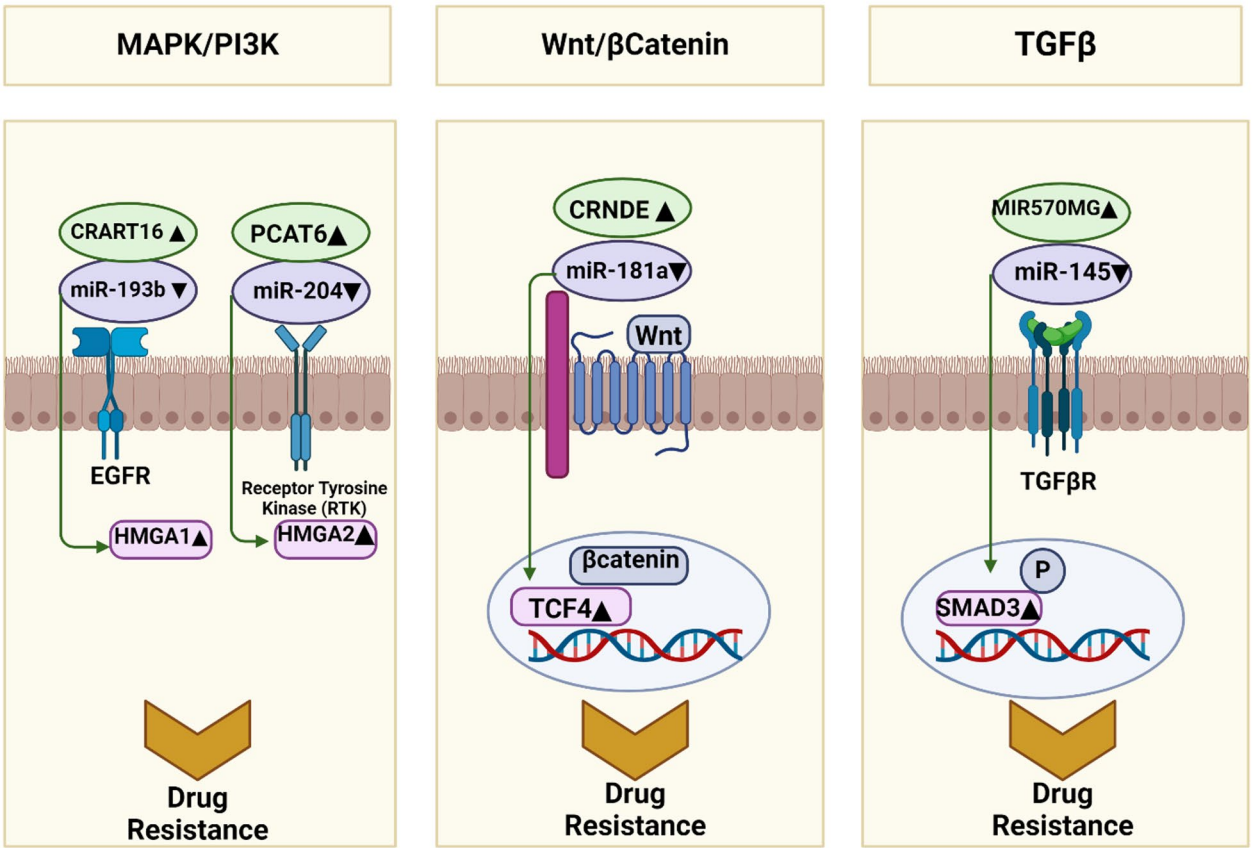

Fig. 3 This figure highlights the interaction between the lncRNA-miRNA-mRNA axis, which influences CRC drug resistance by regulating various signaling pathways

in 5-FU resistance or sensitivity is large and continues to expand, and new miRNAs and mechanisms are being identified [22].

The down-expression of *hsa-miR-543* has been shown to increase the sensitivity of CRC cells to 5-FU through the PTEN/PI3K/AKT pathway [23]. *hsa-miR-23b-3p* increased the sensitivity of 5-FU by down-regulating *ZNF281* in CRC cells [24]. Moreover, *hsa-miR-375-3p* was significantly down-regulated in CRC cell lines and tissues. It enhanced the sensitivity of CRC cells to 5-FU by promoting apoptosis and cell cycle arrest, while also inhibiting cell growth, migration, and invasion in vitro [25]. The *hsa-miR-181d-5p* is a potential therapeutic target for overcoming 5-FU resistance in CRC by modulating its expression or disrupting the *hsa-miR-181d-5p/NCALD* axis. The suppression of *NCALD* by *hsa-miR-181d-5p* disrupts cellular signaling, thereby reducing the efficacy of 5-FU in CRC treatment [26]. Overexpression of *hsa-miR-361* sensitizes resistant CRC cells to 5-FU, induces apoptosis, and acts as a negative regulator of *FOXM1* expression in 5-FU-resistant cells [27]. The *hsa-miR-29b-3p* is involved in resistance to 5-FU-induced necroptosis in CRC. The overexpression of *hsa-miR-29b-3p* is positively correlated with chemoresistance, as it down-regulates *TRAF5*, which reduces necroptosis and enhances cell survival in CRC cells exposed to 5-FU. Conversely, restoring *TRAF5* expression reverses this resistance, positioning *hsa-miR-29b-3p* as a crucial mediator of necroptosis resistance mechanisms and a potential therapeutic target for overcoming 5-FU resistance in CRC treatments [28].

The *hsa-miR-34a*, which is typically induced by functional p53, suppresses the leucine-rich pentatricopeptide repeat-containing protein (LRPPRC). This suppression destabilizes *MDR1* mRNA, a gene associated with multidrug resistance. However, in cases where p53 is inactive or mutated, this regulatory pathway is disrupted, resulting in the stabilization of *MDR1* and an increase in chemoresistance.

Table 1 Some examples of the contribution of MiRNAs in CRC drug resistance through modulating signaling pathways. ▲ Increase ▼ decrease

No.	Drug	miRNA & Alteration	Model Systems	Target/Pathway	Result	Key Validation Assays	Level of Evidence	In ceRNA Network?	Ref
1	5-FU	miR-23b-3p▼	25 5-FU-resistant vs. 25 sensitive CRC tissues; SW480, SW620 cell lines	ZNF281	Promotes 5-FU resistance	In vitro functional assays (OE)/Clinical correlation	Medium	Yes	[24]
2	5-FU	miR-31▲	112 tumor tissues; DLD-1, SW480 cell lines	FIH-1	Promotes 5-FU resistance	In vitro functional assays (OE)/Clinical correlation	Medium	-	[86]
3	5-FU	miR-375-3p▼	367 tumor tissues; HCT116, HT29, SW480, Caco2, and NCM460 cell lines	TYMS	Promotes 5-FU sensitivity	In vitro functional assays (OE)/Clinical correlation	Medium	-	[25]
4	5-FU	miR-34a▼	Colon cancer SP cells; SW480 and LoVo cell lines; 12 female NOD/SCID mice	DLL1/Notch signaling	Promotes 5-FU resistance	In vitro functional assays (OE)/In vivo xenograft validation	Medium	-	[30]
5	5-FU	miR-34a▼	SW480, HCT116 cell lines; male BALB/c nude mice	LRPPRC/MDR1	Promotes 5-FU resistance	In vitro functional assays (OE)/In vivo xenograft validation	Medium	-	[29]
6	5-FU	miR-552▼	97 tumor tissues; SW-480, SW-620, HCT-116, and CCD-18Co cell lines	SMAD2 signaling	Promotes 5-FU resistance	In vitro functional assays (KD)/Clinical correlation	Medium	-	[87]
7	5-FU	miR-29b-3p▲	Multiple CRC cell lines; Male BALB/c NOD mice	TRAF5/necroptosis	Promotes 5-FU resistance	In vitro functional assays (KD)/In vivo xenograft validation	Medium	-	[28]
8	5-FU	miR-17▲	83 tumor tissues; DLD1, HCT16, T84 cell lines	SOX4/CYLD	Promotes 5-FU resistance	In vitro functional assays (OE)/Clinical correlation	Medium	-	[88]
9	5-FU	miR-650▼	80 tumor tissues; SW480 cell line	KISS1	Promotes 5-FU resistance	In vitro functional assays (OE)/Clinical correlation	Medium	-	[89]
10	5-FU	miR-101▼	64 tumor tissues; LoVo, SW620, SW480, HCT-116, and HT-29, CCD-18Co, and HEK293T cell lines	KPNA3	Promotes 5-FU resistance	In vitro functional assays (OE)/Clinical correlation	Medium	-	[91]

Table 1 (continued)

No.	Drug	miRNA & Alteration	Model Systems	Target/Pathway	Result	Key Validation Assays	Level of Evidence	In ceRNA Network?	Ref
11	5-FU	miR-181d-5p▲	30 tumor tissues; HCT116 and HT29 cell lines	NCALD/METTL3	Promotes 5-FU resistance	In vitro functional assays (OE)/Clinical correlation	Medium	-	[26]
12	5-FU	miR-372-3p▼	CCD-18Co, HCT8, HCT116 and SW480 cell lines	EPHA2/LINC02418	Promotes 5-FU sensitivity	RNA-seq data/ In vitro functional assays (OE)	Medium	Yes	[74]
13	5-FU & Oxaliplatin	miR-195-5p ▲ miR-497-5p▲	HCT116, RKO, DLD-1 and SW480 cell lines	CCNE1, WEE1, E2F3	Promotes 5-FU & OXA sensitivity	Proteomic identification/In vitro functional validation (OE)	Medium	-	[41]
14	5-FU & Oxaliplatin	miR-193a-5p▲	68 paired tissues; SW480, LS180, and HT-29 cell lines	CXCR4	Promotes 5-FU & OXA resistance	In vitro functional assays (KD)/Clinical correlation	Medium	-	[40]
15	5-FU	miR-543▼	HCT8 cell line	PTEN PI3K/AKT	Promotes 5-FU sensitivity	In vitro functional assays (OE)	Low	-	[23]
16	5-FU	miR-361▲	HCT116, and HT29 cell lines	FOXM1-ABCC5/10	Promotes 5-FU sensitivity	In vitro functional assays (OE)	Low	-	[27]
17	5-FU	miR-653-3p▲	HCT116, and RKO cell lines	SIRT1/TWIST1	Promotes 5-FU resistance	In vitro functional assays (KD)	Low	-	[90]
18	5-FU	miR-424-5p▼	HT-29 cell line	CCNE1/EMT via Src/ FAK	Promotes 5-FU resistance	In vitro functional assays (OE)	Low	-	[92]
19	5-FU	miR-20b-5p▼	SW480 cell line	SDC2/JNK/ERK	Promotes 5-FU resistance	In vitro functional assays (OE)	Low	-	[93]
20	5-FU & Oxaliplatin	miR-133b▼	HT29, HCT116, SW620 and HEK293 cell lines	DOT1L	Promotes 5-FU & OXA resistance	In vitro functional assays (KD)	Low	-	[39]
21	5-FU & Oxaliplatin	miR-125b-5p▼	HCT116, HCT8 and HT29 cell lines	GLUT5 (SLC2A5)	Promotes 5-FU & OXA resistance	In vitro functional validation (OE)	Low	-	[42]
22	5-FU & Oxaliplatin	miR-15a-5p▲	HCT116 cell line	SIRT4 STAT3/TWIST1 and PTEN/AKT	Promotes 5-FU & OXA resistance	In vitro functional assays (KD)	Low	-	[36]
23	Oxaliplatin	miR-543▲	23 tumor tissues; nude mice; HCT8, and HCT116 cell lines	PTEN/Akt/mTOR	Promotes OXA resistance	In vitro functional assays (OE)/In vivo xenograft model/Clinical correlation	High	-	[32]
24	Oxaliplatin	miR-135b-5p▲	8 tumor tissues; nude mice; SW480, and HCT-116 cell lines	MUL1/ULK1	Promotes OXA resistance	In vitro functional assays (OE)/In vivo xenograft model/Clinical correlation	High	-	[94]

Table 1 (continued)

No.	Drug	miRNA & Alteration	Model Systems	Target/Pathway	Result	Key Validation Assays	Level of Evidence	In ceRNA Network?	Ref
25	Oxaliplatin	miR-454-3p▼	45 tumor tissues; nude mice; HCT-116 cell line	PTEN/AKT	Promotes OXA sensitivity	In vitro functional assays (OE)/In vivo xenograft model/Clinical correlation	High	-	[35]
26	Oxaliplatin	miR-31-5p▲	LoVo cell line; nude mice	LATS2 & FOXC1	Promotes OXA resistance	In vitro functional assays (KD)/In vivo xenograft validation	Medium	-	[31]
27	Oxaliplatin	miR-200b-3p▲	10 OXA resistance vs. 13 non- OXA resistance patient tissues; HT29, and HCT116 cell lines	TUBB3	Promotes OXA resistance	In vitro functional assays (OE)/Clinical correlation	Medium	-	[33]
28	Oxaliplatin	miR-29a-3p▲	Nude mice; LoVo cell line	Fem1B/Gli1	Promotes OXA resistance	miRNA array/In vitro functional assays (KD)/In vivo xenograft model	Medium	-	[95]
29	Oxaliplatin & FOLFOX	miR-208b▲	116 tumor tissues; Murine CT26 cells; SW480-OXA	PDCD4	Promotes OXA & FOLFOX sensitivity	In vitro functional assays (OE)/Clinical correlation	Medium	-	[34]
30	Oxaliplatin	miR-483-3p▼	HCT116, LOVO, and SW480 cell lines	FAM171B	Promotes OXA resistance	In vitro functional assays (OE)	Low	-	[37]
31	Oxaliplatin	miR-409-3p▼	HCT-116 cell line	ERCC1	Promotes OXA resistance	In vitro functional assays (OE)	Low	-	[38]
32	Oxaliplatin	miR-46,146▲	HCT116, and HT29 cell lines	PDCD10	Promotes OXA resistance	In vitro functional assays (KD) (preliminary)	Low	-	[96]
33	Cetuximab	miR-302a▼	20 tumor tissues; nude mice; 13 + CRC cell lines	NFIB, CD44	Promotes CTX resistance	Extensive in vitro functional assays (OE)/In vivo xenograft validation/Clinical correlation	High	-	[47]
34	Cisplatin	miR-148a▲	90 tumor tissues; nude mice; SW480 Cell line	WNT10b/β-catenin	Promotes Cisplatin sensitivity	In vitro functional assays (OE)/In vivo xenograft model/Clinical correlation	High	-	[97]

Table 1 (continued)

No.	Drug	miRNA & Alteration	Model Systems	Target/Pathway	Result	Key Validation Assays	Level of Evidence	In ceRNA Network?	Ref
35	Cetuximab	miR-199b-3p▲	30 tumor tissues; Multiple CTX resistant and parental cell lines	CRIM1/Wnt/β-catenin	Promotes CTX resistance	In vitro functional assays (KD)/Clinical correlation	Medium	-	[49]
36	Cetuximab	miR-141-3p▲	HCT-15, and SW48 cell lines	EGFR/EMT	Promotes CTX sensitivity	In vitro functional assays (OE)	Low	-	[48]

Abbreviations: 5-FU, 5-fluorouracil; OXA, Oxaliplatin; CTX, Cetuximab; CRC, Colorectal Cancer; SP, Side Population; OE, Overexpression; KD, Knockdown; EMT, Epithelial-Mesenchymal Transition; qPCR, Quantitative Polymerase Chain Reaction; RNA-seq, RNA sequencing

Level of Evidence was defined as follows:

· High: In vitro functional assays (OE/KD) + in vivo xenograft validation with chemotherapeutic agent + clinical correlation

· Medium: In vitro functional assays with supporting clinical expression data or multi-model validation, but lacking in vivo drug response data

· Low: Primarily dysregulation data with preliminary functional validation in limited models (e.g., a single cell line), without strong clinical or in vivo correlation

Also, targeting LRPPRC with specific inhibitors such as gossypol-acetic acid (GAA) can restore chemosensitivity to 5FU in p53-inactive CRC models, both in vitro and in vivo. These findings emphasize the potential of the hsa-miR-34a/LRPPRC/MDR1 axis as a therapeutic target for overcoming chemoresistance in CRC [29]. It is important to note that *hsa-miR-34a* was significantly downregulated in the side population (SP) cells of colon cancer. Furthermore, the overexpression of *hsa-miR-34a* can overcome drug resistance to 5-FU, indicating that this miRNA functions as a tumor suppressor by enhancing chemosensitivity to 5-FU in SP cells. The *hsa-miR-34a* targets and suppresses the expression of *DLL1*, a ligand in the Notch signaling pathway, which is a key regulator of ABCG2. This suppression disrupts the pathway, reducing drug resistance. Furthermore, increasing *hsa-miR-34a* levels not only reverses resistance to 5-FU in vitro but also inhibits tumor growth under 5-FU treatment in vivo, demonstrating its potential as a therapeutic target for addressing chemotherapy resistance in CRC [30].

Evidence for several miRNAs, such as *hsa-miR-34a*, *hsa-miR-23b-3p*, and *hsa-miR-375-3p*, is relatively consistent, suggesting a stronger role in modulating the response to 5-FU. In contrast, signals involving *hsa-miR-181d-5p* and *hsa-miR-29b-3p* are less well established and remain preliminary. Further replication in independent cohorts and functional validation in clinical models are required before these miRNAs can be translated into clinical practice.

MiRNAs related to oxaliplatin resistance

Oxaliplatin (OXA) is commonly used for the treatment of colorectal carcinoma. However, the development of resistance can lead to tumor recurrence, rendering them insensitive to OXA.

Some miRNAs are specifically associated with sensitivity to OXA, while others are linked to drug resistance. This suggests a complex interplay between various miRNA species and the cellular response to OXA treatment. Among the miRNAs that contribute to cellular sensitivity to OXA, *hsa-miR-31-5p* is notable. This miRNA regulates the sensitivity of CRC cells to OXA by targeting the *LATS2* gene, which results in tumor proliferation and modulation of sensitivity to OXA-based chemotherapy [31].

Also, the upregulation of *hsa-miR-543* has been associated with increased cell sensitivity to OXA, although this miRNA is expressed at higher levels in chemoresistant CRC cells compared to chemosensitive ones [32]. Similarly, the overexpression of *hsa-miR-200b-3p* has been shown to enhance OXA sensitivity in OXA-resistant cells [33].

Additionally, the upregulation of *hsa-miR-208b* promotes the expansion of regulatory T cells (Tregs) by targeting *PDCD4*, which may be related to decreased OXA-based chemosensitivity in CRC [34]. Furthermore, the overexpression of *hsa-miR-454-3p* has been found to decrease the sensitivity of HCT-116 xenograft tumors to OXA treatment in a mouse model [35].

The *miR-15a-5p/SIRT4* axis has also been reported to enhance the sensitivity to 5-FU in oxaliplatin-resistant cells [36]. Furthermore, the downregulation of *hsa-miR-483-3p*, accompanied by the upregulation of *FAM171B*, has been associated with increased sensitivity to OXA and decreased cell migration in OXA-resistant CRC cell lines [37].

The mechanism of action related to curcumin's regulation of *ERCC1* expression was investigated, and it was found to increase OXA sensitivity through its effects on *hsa-miR-409-3p*, the low expression of which may promote drug resistance in human CRC-resistant cells [38].

The overexpression of *hsa-miR-133b* reduced CRC stemness and overcame resistance to both 5-FU and OXA

[39]. Additionally, *hsa-miR-193a-5p* and *hsa-miR-15a-5p* are both up-regulated in CRC cells treated with 5-FU and OXA [36, 40]. Furthermore, *hsa-miR-195-5p* and *hsa-miR-497-5p* have been shown to increase sensitivity to OXA and to a lesser extent, sensitivity to 5-FU [41].

In OXA- and in 5-FU-resistant colon cancer cells, the suppression of *hsa-miR-125b-5p* leads to increased *GLUT5* expression and enhanced cancer cell migration. This occurs through the promotion of fatty acid synthesis and lactate production, indicating that *hsa-miR-125b-5p* levels are reduced in 5-FU and in OXA-resistant cells [42].

Among OXA-associated miRNAs, *hsa-miR-31-5p* and *hsa-miR-200b-3p* emerge as the most consistently replicated findings across studies. Other candidates, such as *hsa-miR-208b* and *hsa-miR-454-3p*, are supported by limited or conflicting evidence. Overall, distinguishing reliable regulators from preliminary signals remains a critical step in advancing these observations toward clinical application.

MiRNAs related to Irinotecan resistance

Irinotecan resistance poses a significant challenge in cancer treatment, particularly in CRC and other gastrointestinal malignancies. *hsa-miR-200* can enhance the chemosensitivity of CRC cells to irinotecan [43].

Data obtained from differentially expressed genes (DEGs) using the miRTarBase database highlight the critical roles of *hsa-miR-335* and *hsa-miR-124* in regulating several key downregulated DEGs that are common across irinotecan-resistant CRC cell line samples [44].

Research on irinotecan resistance remains in its early stages. While *hsa-miR-200* has some functional evidence supporting its involvement, the data regarding *hsa-miR-335* and *hsa-miR-124* are primarily exploratory. Larger sample sizes, animal models, and clinical confirmation are needed to determine whether these miRNAs play a genuine role in irinotecan response.

MiRNAs related to FOLFOX resistance

FOLFOX is a cornerstone regimen for patients' candidate for adjuvant chemotherapy or in cases of recurrence and metastasis, in this case associated with monoclonal antibodies [45, 46]. The differential expression profiles of circulating miRNAs have been analyzed in response to FOLFOX therapy in CRC patients. The findings indicated that the expression levels of circulating miRNAs in non-responders were higher than in responders before treatment, suggesting that the association of these miRNAs increased drug resistance and poor clinical outcomes. Specifically, the expression of *hsa-miR-208b* was significantly altered after chemotherapy, with its level decreased in patients who responded to FOLFOX but increased in patients who did not respond to this regimen, suggesting that serum *hsa-miR-208b* may serve as a non-invasive marker to predict FOLFOX chemosensitivity in CRC [34].

Circulating miRNAs, such as *hsa-miR-208b*, show promise as non-invasive predictors of FOLFOX sensitivity. However, current findings are mostly preliminary and occasionally inconsistent. To date, there is insufficient clinical validation, highlighting the need for prospective studies before these markers can be considered reliable.

MiRNAs related to cetuximab resistance

Cetuximab (CTX), a monoclonal antibody targeting EGFR, is recommended for mCRC. Some studies have identified an important role for miRNAs in regulating metastasis and CTX resistance, with prognostic and therapeutic implications in CRC. *hsa-miR-302a* has been found to act as a multifaceted regulator of CRC metastasis and CTX resistance by targeting *NFIB* and *CD44*, respectively [47].

Additionally, *hsa-miR-141-3p* enhanced cetuximab-induced apoptosis in CRC cells and could predict cetuximab sensitivity by directly targeting the EGFR signaling pathway [48]. Furthermore, *hsa-miR-199b-3p* expression was associated with acquired resistance to CTX in CRC, and the CRIM1/Wnt/β-catenin signaling is involved in *hsa-miR-199b-3p*-mediated CTX resistance [49].

hsa-miR-302a and *hsa-miR-141-3p* represent relatively stronger signals, having been repeatedly linked with cetuximab resistance and sensitivity, respectively. On the other hand, findings for *hsa-miR-199b-3p* and other miRNAs remains limited, rendering their clinical relevance uncertain. Further comparative studies across patient datasets are essential to confirm these associations.

MiRNAs related to bevacizumab resistance

MicroRNAs play a significant role in mediating resistance to the antiangiogenic bevacizumab, a drug utilized in several cancers including CRC. Both *hsa-miR-126-3p* and *hsa-miR-126-5p* are closely linked to the regulation of angiogenesis. Low expression levels of *hsa-miR-126-3p* are associated with reduced survival and resistance to bevacizumab, whereas higher levels correlate with improved treatment outcomes [50]. Additionally, *hsa-miR-7-5p* and *hsa-miR-10a-5p* have been identified as potential resistance markers to bevacizumab. Elevated expression levels of these miRNAs are associated with poorer progression-free survival (PFS) and OS in non-responders to the treatment. In contrast, *hsa-miR-143-3p* is linked to better outcomes, as its higher expression correlates with improved PFS and a favorable prognosis. This suggests that overexpression of

hsa-miR-7-5p and *hsa-miR-10a-5p* may indicate a lack of response to treatment regimens including bevacizumab in patients with mCRC, while *hsa-miR-143-3p* could serve as a marker for a more favorable therapeutic response [51].

The role of *hsa-miR-126-3p* in regulating angiogenesis and the response to bevacizumab is supported by multiple lines of evidence and appears to be more reliable. In contrast, miRNAs such as *hsa-miR-7-5p* and *hsa-miR-10a-5p* have been linked to resistance mainly in preliminary studies, and their predictive value remains unclear. Although *hsa-miR-143-3p* is a promising candidate, it still requires further validation in clinical settings.

LncRNAs regulate drug resistance in CRC

Numerous studies have investigated the role of various lncRNAs and their interactions with molecular components, including miRNAs and other RNA types, in mediating CRC resistance to cytotoxic and targeted therapeutic agents [52–54]. However, current evidence remains insufficient to designate these lncRNAs as definitive mediators of chemoresistance. Most recent studies in this field are listed in Table 2. In this section, the studies are comparatively assessed to clarify the relative strength of evidence and identify remaining knowledge gaps.

LncRNAs related to 5-FU resistance

In a study conducted by Gao, Ren et al., the upregulated *FGD5-AS1* lncRNA was shown to contribute to 5-FU resistance through the EGFR–FGD5-AS1–miR-330-3p–HK2 pathway [55]. This evidence, derived from CRC tissues, cell lines, and xenograft models, enhances the translational reliability of the results, though confirmation in independent studies is still required.

The Fu, Huang et al. study found that the downregulation of *OXR1-1:3* lncRNA was associated with 5-FU drug resistance. Although, the investigation was conducted both in vitro and in vivo, potential miRNA and other regulatory genes were not considered. Thus, further comprehensive and mechanistic evaluation of this result is needed [56]. Additional analyses are needed to explore its downstream targets and determine whether this association reflects a causal relationship.

Jiang, Li et al. investigated the HAND2-AS1/miR-20a/PDCD4 regulatory axis and confirmed its role in mediating 5-FU resistance across tumor tissues, in vitro, and in vivo experiments [57]. The data provide strong, albeit confirmatory, evidence that *HAND2-AS1* modulates chemoresistance and warrants further validation in larger cohorts.

Overall, current findings suggest that 5-FU resistance in CRC induced by lncRNAs is commonly linked to their upregulation. Among these, *HAND2-AS1* shows the most consistent validation, whereas evidence for *FGD5-AS1* and *OXR1-1:3* remains preliminary, emphasizing the need for further systematic and mechanistic studies.

LncRNAs related to OXA resistance

It has been accepted that ncRNAs mediate chemoresistance to OXA in different stages in the cells like in transcriptional and post-transcriptional regulation, and also by epigenetic modification. In addition, lncRNAs contribute to drug transport, tumor progression, and delayed cell death by regulating multiple signaling cascades [58, 59].

Gao, Fang, et al. conducted a study that identified the involvement of the upregulated *CACS15* lncRNA in OXA drug resistance. Besides, the study revealed the roles of the *ABCC1* gene and *hsa-miR-145* in this process [60].

More recently, Zhu et al. identified the upregulation of *FAL1* as a contributor to oxaliplatin resistance in CRC, supported by results from both cellular and animal studies [61]. Nevertheless, broader validation remains necessary to confirm its relevance.

Taken together, current evidence indicates that *CACS15* and *FAL1* may play roles in oxaliplatin resistance; however, the current data are limited and heterogeneous. Larger and independent validations are needed to determine whether these lncRNAs serve as reliable biomarkers or mechanistic mediators of resistance (Table 2).

LncRNAs related to Irinotecan resistance

LncRNAs, such as *HOTAIR*, *UCA1*, *CRNDE*, and *H19*, play critical roles in mediating resistance to irinotecan in CRC. These lncRNAs regulate essential processes, including apoptosis, angiogenesis, and tumor metabolism, which diminish the efficacy of SN-38, the active metabolite of irinotecan. Elevated expression levels of *HOTAIR* and *UCA1* are strongly correlated with poor prognosis and resistance through mechanisms such as drug efflux and the activation of survival pathways. Similarly, *CRNDE* and *H19* contribute to resistance by modulating gene networks and influencing the tumor microenvironment. Collectively, these findings suggest that targeting lncRNAs involved in irinotecan resistance may serve as a promising therapeutic approach for overcoming irinotecan resistance and improving treatment outcomes in CRC [62, 63]. *UCA1* and *HOTAIR* have shown the most consistent association with irinotecan resistance, supported by functional assays and clinical correlations, highlighting their potential as reliable indicators in CRC.

Table 2 Some examples of the contribution of LncRNAs in CRC drug resistance through modulating signaling pathways. ▲ Increase ▼ decrease

No.	Drug	lncRNA & Alteration	Model Systems	Target/Pathway	Result	Key Validation Assays	Level of Evidence	In ceRNA Network?	Ref
1	5-FU	HAND2-AS1 ▼	50 tumor tissues; nude mice; SW480, NCM460, HCT116 cell lines	miR-20a/PDCD4	Promotes 5-FU resistance	In vitro functional assays (OE)/ In vivo xenograft model/ Clinical correlation	High	Yes	[57]
2	5-FU	UCA1▲	25 resistant vs. 25 sensitive tissues; nude mice, SW480, SW620, and 293 T cell lines	miR-23b-3p/ZNF281	Promotes 5-FU resistance	In vitro functional assays (KD)/ In vivo xenograft model/ Clinical correlation	High	Yes	[98]
3	5-FU	FGD5-AS1▲	40 resistant vs. 40 sensitive tissues; nude mice, LoVo, HCT-116, HT-29, and DLD-1 cell lines	miR-330-3p/HK2	Promotes 5-FU resistance	In vitro functional assays (KD)/ In vivo xenograft model/ Clinical correlation	High	Yes	[55]
4	5-FU	NEAT1▲	30 paired tissues, BALB/c-nude mice, SW480, HCT116 and NCM460 cell lines	miR-150-5p/CPSF4	Promotes 5-FU resistance	In vitro functional assays (KD)/ In vivo xenograft model/ Clinical correlation	High	Yes	[99]
5	5-FU	SNHG6▲	31 paired tissues, BALB/c nude mice, RKO, HT29 SNHG6 cell lines and HCT116 cell lines	miR-26a-5p/ULK1 (Autophagy)	Promotes 5-FU resistance	In vitro functional assays (KD)/ In vivo xenograft model/ Clinical correlation	High	Yes	[100]

Table 2 (continued)

No.	Drug	lncRNA & Alteration	Model Systems	Target/Pathway	Result	Key Validation Assays	Level of Evidence	In ceRNA Network?	Ref
6	5-FU	LBX2-AS1▲	256 tumor tissues; nude mice, and HCT116 and SW480 cell lines	miR-422a/AKT1	Promotes 5-FU resistance	In vitro functional assays (KD)/ In vivo xenograft model/ Clinical correlation	High	Yes	[77]
7	5-FU	DLGAP1-AS1▲	42 paired tissues, nude mice, LoVo, HT-29, SW480, and HCT116 cell lines	miR-149-5p/TGFB2 (TGFB signaling)	Promotes 5-FU resistance	In vitro functional assays (KD)/ In vivo xenograft model/ Clinical correlation	High	Yes	[101]
8	5-FU	CCAT1▲	67 tumor tissues, BALB/c mice, HCT 116, SW1417, HT-29, KM12 and NCM460 cell lines	miR-218, −143, −152/c-Myc (Apoptosis)	Promotes 5-FU sensitivity	In vitro functional assay (KD) demonstrating sensitization/In vivo xenograft model/ Clinical correlation	High	Yes	[105]
9	5-FU	POU6F2-AS2▲	70 paired tissues, nude mice, HT-29, HCT-116, SW620, OUMS23 and NCM460 cell lines	miR-377/BRD4	Promotes 5-FU sensitivity	In vitro functional assays (KD) demonstrating sensitization/In vivo xenograft model/ Clinical correlation	High	Yes	[76]
10	5-FU	TUG1▲	124 paired tissues, HCT8Fu, HCT8, HCT116, and SW1116 cell lines	miR-197-3p/TYMS	Promotes 5-FU resistance	In vitro functional assays (KD)/ Clinical correlation	Medium	Yes	[103]
11	5-FU	PCAT6▲	73 paired tissues, multiple CRC and normal cell lines	miR-204/HMGA2 (PI3K signaling)	Promotes 5-FU resistance	In vitro functional assays (KD)/ Clinical correlation	Medium	Yes	[104]

Table 2 (continued)

No.	Drug	lncRNA & Alteration	Model Systems	Target/Pathway	Result	Key Validation Assays	Level of Evidence	In ceRNA Network?	Ref
12	5-FU	CRART16▲	HEK-293T, SW620, Caco-2 cell lines	miR-193b-5p/HMGA1 (MAPK signaling)	Promotes 5-FU resistance	In vitro functional assays (KD)	Low	Yes	[102]
13	Oxaliplatin	XIST ▲	122 tumor tissues, BALB/c nude mice/ DLD1, HCT116, HCT8, Cell lines	miR-125b-2-3p/Wee1	Promotes OXA resistance	In vitro functional assays (KD)/ In vivo xenograft model/ Clinical correlation	High	Yes	[106]
14	Oxaliplatin	CACS15▲	96 paired tissues, BALB/c-nude mice, NCM460, HT29, HCT116 cell lines	miR-145/ABCC1	Promotes OXA resistance	In vitro functional assays (KD)/ In vivo xenograft model/ Clinical correlation	High	Yes	[60]
15	Oxaliplatin	KCNQ1OT1▲	90 paired tissues, BALB/c nude mice, HCT116 and SW480 cell lines	miR-34a/ATG4B pathway	Promotes OXA resistance	In vitro functional assays (KD)/ In vivo xenograft model/ Clinical correlation	High	Yes	[79]
16	Oxaliplatin	MCF2L-AS1▲	120 tumor tissues, BALB/c nude mice and HT-29, LOVO cell lines	miR-105/IL-1β	Promotes OXA resistance	In vitro functional assays (KD)/ In vivo xenograft model/ Clinical correlation	High	Yes	[107]
17	Oxaliplatin	Linc00152▲	134 paired tissues, Nude mice, NCM460, SW480, Caco2, SW620, and HT29 cell lines	miR-193a-3p/ERBB4 (AKT signaling)	Promotes OXA resistance	In vitro functional assays (KD)/ In vivo xenograft model/ Clinical correlation	High	Yes	[108]

Table 2 (continued)

No.	Drug	lncRNA & Alteration	Model Systems	Target/Pathway	Result	Key Validation Assays	Level of Evidence	In ceRNA Network?	Ref
18	Oxaliplatin	MALAT1 ▲	40 resistant vs. 40 sensitive tissues, nude BALB/c mice, and HCT116 and HCT8 cell lines	miR-324 3p/ADAM17	Promotes OXA resistance	In vitro functional assays (KD)/ In vivo xenograft model/ Clinical correlation	High	Yes	[109]
19	Oxaliplatin	HOTAIR ▲	BALB/c nude mice, LoVo, HT-29, and HCT-116cell lines	miR-1277-5p/ZEB1	Promotes OXA resistance	In vitro functional assays (KD)/ In vivo xenograft model	High	Yes	[110]
20	Oxaliplatin	BLACAT1▲	55 tumor tissues, BALB/c-nude mice, HIEC-6, HCT116, HT29, LOVO, and SW620 cell lines	miR-519d-3p/CREB1	Promotes OXA resistance	In vitro functional assays (KD)/ In vivo xenograft model/ Clinical correlation	High	Yes	[111]
21	Oxaliplatin	MALAT1 ▲	68 paired tissues, and HT29, SW480, SW620, FHC cell lines	miR-218/EZH2	Promotes OXA resistance	In vitro functional assays (KD)/ Clinical correlation	Medium	Yes	[112]
22	Oxaliplatin	LINC00525▲	60 fresh paired tissues, Caco2, SW480, SW620, HCT116 and HT29 cell lines	miR-507/ELK3	Promotes OXA resistance	In vitro functional assays (KD)/ Clinical correlation	Medium	Yes	[113]
23	Oxaliplatin	CRNDE ▲	64 tumor tissues, HCT116 and SW480 cell lines	miR-181a-5p/TCF4 (Wnt/β-catenin)	Promotes OXA resistance	In vitro functional assays (KD)/ Clinical correlation	Medium	Yes	[114]

Table 2 (continued)

No.	Drug	lncRNA & Alteration	Model Systems	Target/Pathway	Result	Key Validation Assays	Level of Evidence	In ceRNA Network?	Ref
24	Cetuximab	HCG18▲	33 paired tissues, BALB/c nude mice, HT29, SW480 and LOVO cell lines	miR-20b-5p/PD-L1	Promotes CET resistance	In vitro functional assays (KD)/ In vivo xenograft model/ Clinical correlation	High	Yes	[116]
25	Cetuximab	UCA1▲	20 paired tissues, BALB/c athymic nude mice, Caco2 cell line	miR-495/HGF/c-MET	Promotes CET resistance	In vitro functional assays (KD)/ In vivo xenograft validation/ Clinical correlation	High	Yes	[117]
26	Cetuximab	MIR100HG ▲	Extensive cell line panel, athymic BALB/c nude mice	miR-100, −125b/GATA6 (Wnt/β-catenin)	Promotes CET resistance	In vitro functional assays (KD)/ In vivo xenograft validation	Medium	Yes	[118]
27	Cetuximab	HCG18▲	20 paired tissues, CCC-HIE-2, SW480, SW620, SW48, HCT116, LoVo and HCT-15 cell lines	miR-365a-3p/FOXO1	Promotes CET resistance	In vitro functional assays (KD)/ Clinical correlation	Medium	Yes	[81]
28	Cetuximab	CRART16▲	HCT116, HT29, HCT8, SW620 and Caco-2 cell lines	miR-371a-5p/ERBB3 (Apoptotic pathway)	Promotes CET resistance	In vitro functional assays (KD)	Low	Yes	[115]

Table 2 (continued)

No.	Drug	lncRNA & Alteration	Model Systems	Target/Pathway	Result	Key Validation Assays	Level of Evidence	In ceRNA Network?	Ref
29	Bevacizumab	SNHG11 ▲	27 paired tissues, nude mice, NCM460, LOVO and HCT116 cell lines	miR-1207-5p/ABCC1	Promotes Bevacizumab resistance	In vitro functional assays (KD)/ In vivo xenograft model/ Clinical correlation	High	Yes	[80]
30	Regorafenib	MIR570MG ▲	Nude mice and SW480 and HCR116 cell lines	miR-145/SMAD3 signaling	Promotes REG resistance	In vitro functional assays (KD)/ In vivo xenograft validation	Medium	Yes	[82]

Abbreviations: lncRNA, long non-coding RNA; 5-FU, 5-fluorouracil; OXA, Oxaliplatin; CET, Cetuximab; CRC, Colorectal Cancer; OE, Overexpression; KD, Knockdown;

Level of Evidence was defined as follows:

· High: In vitro functional assays (OE/KD) + in vivo xenograft validation with chemotherapeutic agent + clinical correlation

· Medium: In vitro functional assays with supporting clinical expression data or multi-model validation, but lacking in vivo drug response data

· Low: Primarily dysregulation data with preliminary functional validation in limited models (e.g., a single cell line), without strong clinical or in vivo correlation

In contrast, *CRNDE* and *H19* have been reported mainly in exploratory studies, and their functional relevance remains to be fully validated. Overall, while several lncRNAs exhibit potential clinical relevance, only a limited subset currently provides reproducible evidence sufficient to support their use as robust indicators of irinotecan resistance (Table 2).

LncRNAs related to bevacizumab resistance

Despite thorough evaluation of OXA and 5-FU drug resistance, bevacizumab drug resistance has not been studied sufficiently, highlighting the need for additional research to determine the potential effect of lncRNAs and other ceRNA, including miRNA and genes, on this event [64].

The only comprehensive study on this topic is the investigation by Huang et al., which focused on.

the hsa-miR-1207-5p/ABCC1 axis. The study encompassed CRC tissues, cell lines, and xenograft models, providing multi-level validation but still requiring independent confirmation. The results demonstrated that lncRNA *SNHG11* was upregulated, and *hsa-miR-1207-5p* was downregulated in bevacizumab-resistant cells.

Currently, the available evidence remains limited, with *SNHG11* being the only lncRNA investigated in detail. Although Huang et al. provided in vitro, in vivo, and clinical validation, replication remains limited. As summarized in Table 2, current evidence supports *SNHG11* as a potential regulator of bevacizumab resistance, but further multi-level validation is required to confirm its clinical relevance.

LncRNAs related to cetuximab resistance

Recent advances in understanding cetuximab resistance in CRC have highlighted lncRNAs, particularly *UCA1*, as key players in cancer progression and drug resistance. *UCA1* regulates critical pathways, including EGFR signaling, targeted by cetuximab. Its altered expression supports feedback loops that sustain tumor growth and survival despite therapy. Beyond intracellular signaling, *UCA1* impacts the tumor microenvironment by influencing immune cell infiltration and stromal interactions, further driving resistance. Moreover, it has also been implicated in resistance to other therapies, such as irinotecan, suggesting its role as a convergence point for multiple drug resistance mechanisms.

Targeting *UCA1* or its downstream effectors through RNA-based inhibitors or small molecules offers promising strategies to overcome resistance and enhance cetuximab efficacy. These findings position *UCA1* as a biomarker and a therapeutic target in CRC treatment [65, 66].

Experimental evidence supports the involvement of *UCA1* in cetuximab resistance through the miR-495/HGF/c-MET axis, validated across cellular and animal models. Among known lncRNAs, *UCA1* stands out as the most consistently supported by both experimental and clinical evidence (Table 2). In contrast, *CRART16*, *MIR100HG*,

and *HCG18* remain underexplored, with validation limited mainly to in vitro studies. Further multicenter investigations are needed to confirm the robustness of *UCA1* across patient populations.

LncRNAs related to regorafenib resistance

The mechanisms of CRC resistance to regorafenib have not been widely assessed, and to better illuminate this underexplored area, more efforts are needed to evaluate the effect of lncRNAs on regorafenib tumor resistance [67].

Previous studies on this topic are limited, with the following being the most comprehensive. The study by Q. Wen et al. primarily focused on the αvβ3-integrin/FAK/PI3K/AKT pathway, investigating the role of the *SYTL5-OT4* lncRNA and *ASCT2* gene in drug resistance. Their findings demonstrated that *SYTL5-OT4* lncRNA and *ASCT2* gene were both overexpressed under chemoresistance conditions [68].

Although these findings reveal a novel regulatory mechanism, current evidence is derived from a single study and remains preliminary. Broader validation in patient-derived and multicenter models is essential to determine whether *SYTL5-OT4* represents a reproducible biomarker of regorafenib resistance. To date, no lncRNA has entered clinical evaluation in colorectal cancer, in contrast to microRNAs that dominate noncoding RNA–based trials. This lack of clinical progression underscores the technical and biological challenges that continue to impede the translation of lncRNA discoveries into therapeutic applications.

CircRNAs related to drug resistance in CRC

The distinct characteristics and biological roles of circRNAs underscore their significance in tumor development, growth, metastasis, invasion, and resistance to drugs and radiation. Moreover, these findings suggest that circRNAs may serve as potential biomarkers or therapeutic targets related to drug resistance in tumors [69]. The most prominent studies related to drug resistance and circRNAs are discussed and several studies that identified specific circRNAs associated with drug resistance in CRC are summarized in Table 3; Fig. 3.

CircRNAs related to 5-FU resistance

The investigation of various circRNAs reveals several key findings related to CRC progression and resistance to 5-FU. One of the most robust findings is the role of *circ_0014130*, which promotes CRC progression by acting as a sponge for *hsa-miR-197-3p*, thereby positively regulating *PFKFB3*. Its impact on enhancing resistance to 5-FU has been consistently replicated across studies, indicating that targeting *circ_0014130* could significantly improve the sensitivity of CRC tissues to 5-FU, underscoring its clinical relevance. Similarly, *circ_0000338* has been implicated in 5-FU resistance through its negative regulation of *hsa-miR-217* and *hsa-miR-485-3p* via exosomal pathways. This finding not only suggests its involvement in chemosensitivity but also points to *circ_0000338* as a potential biomarker for guiding 5-FU-based chemotherapy in clinical settings. The reproducibility of these results enhances their reliability. Another significant finding involves *circ-ERBB2*, where knockdown experiments have consistently demonstrated that it promotes sensitivity to 5-FU by modulating the miR-181a-5p/PTEN/Akt pathway. This provides robust evidence for its role as a valuable biomarker for CRC diagnosis and treatment. Furthermore, *circDDX17* has been identified as a regulator of chemosensitivity to 5-FU, with its upregulation associated with blocking CRC progression through the miR-31-5p/KANK1 axis. The replicability of these findings strengthens their significance, suggesting that *circDDX17* could be an important target in CRC therapy. Overall, these findings regarding these circRNAs not only demonstrate robustness and replication across various studies but also highlight their potential clinical relevance in enhancing treatment strategies for CRC patients resistant to 5-FU.

CircRNA related to oxaliplatin resistance

hsa_circ_0079662, a circRNA that binds with *hsa-mir-324-5p* and affects the growth, migration, and invasion of CRC cells, can also regulate the target gene *HOXA9* and the mechanism of resistance to OXA through TNF-α pathway in human colon cancer [70]. The expression of *circPDE4D* is significantly increased in OXA-resistant CRC cells. Also, this circRNA is a potent ceRNA that targets *hsa-miR-569* and regulates the expression of SPl1, effectively inhibiting tumorigenesis and progression of both normal and resistant CRC cells [71].

Overall, both circRNAs present robust findings that warrant further investigation for their implications in CRC treatment and resistance.

CircRNA related to cetuximab resistance

Recent research found that *circHIF1A* is significantly overexpressed in cetuximab-resistant LIM1215-R cell lines compared to their cetuximab-sensitive counterparts, LIM1215 cells. This finding is robust, as it suggests a clear link between *circHIF1A* levels and drug resistance. Furthermore, reducing *circHIF1A* in resistant cells results in notable outcomes: a decrease in cell proliferation and clonal formation, an increased proportion of cells in the G0-G1

Table 3 Some examples of the contribution of circrna in CRC drug resistance through modulating signaling pathways. ▲ Increase ▼ decrease

No.	Drug	CircRNAs & Alteration	Model Systems	Target/pathway	Result	Key Validation Assays	Level of Evidence	In ceRNA Network?	ref
1	5-FU	circ_0014130▼	57 paired tissues, BALB/c nude mice, NCM460, HCT116 and LoVo cell lines	miR-197-3p/PFKFB3	Promotes 5-FU resistance	In vitro functional assays (OE)/ In vivo xenograft model/ Clinical correlation	High	Yes	[119]
2	5- FU	circ_0000338 ▲	60 tumor tissues, 15 BALB/C nude mice, SW480, HCT116 cell lines	EMT pathway	Promotes 5-FU resistance	In vitro functional assays (KD)/ In vivo xenograft model/ Clinical correlation	High	-	[120]
3	5- FU	circ_0007031 ▼	60 tumor tissue, 18 BALB/c nude mice, SW480, HCT116 cell lines	miR-133b/ABCC5	Promotes 5-FU sensitivity	In vitro functional assays (OE)/ In vivo xenograft model/ Clinical correlation	High	Yes	[121]
4	5- FU	circ-ERBB2 ▼	NCM460, SW480 and HCT116 cell lines	PTEN/Akt pathway	Promotes 5-FU sensitivity	In vitro functional assays (KD)/ Clinical correlation	Medium	-	[122]
5	5- FU & Oxaliplatin	circ-ZEB1 ▲	44 paired tissues, BALB/c nude mice, SW480 and RKO cell lines	EMT	Promotes 5-FU resistance	In vitro functional assays (KD)/ In vivo xenograft model/ Clinical correlation	High	-	[123]
6	5- FU	circ-0004771 ▲	60 serum and tumor tissues, 60 controls, multiple CRC cell lines	miR-653/ZEB2	Promotes 5-FU resistance	In vitro functional assays (KD)/ Clinical correlation	Medium	Yes	[124]
7	5- FU	circDDX17 ▲	30 paired tissues, BALB/c nude mice, NCM460, SW480 and HCT116 cell lines	miR-31-5p/KANK1	Promotes 5-FU sensitivity	In vitro functional assays (KD)/ In vivo xenograft model/ Clinical correlation	High	Yes	[125]
8	5- FU	circ-PRKDC ▲	30 resistant vs. sensitive tissues, Nude mice, FHC, SW620, SW480 cell lines	miR-375/FOXM (Wnt/β-Catenin)	Promotes 5-FU resistance	In vitro functional assays (KD)/ In vivo xenograft model/ Clinical correlation	High	Yes	[126]

Table 3 (continued)

No.	Drug	CircRNAs & Alteration	Model Systems	Target/pathway	Result	Key Validation Assays	Level of Evidence	In ceRNA Network?	ref
9	5- FU	circSAMD4A ▲	74 tumor tissues, BALB/c nude Mice, SW480, HCT-116, SW480/5-Fu and HCT-116/5-Fu cell lines	miR-545-3p/PFKFB3	Promotes 5-FU resistance	In vitro functional assays (KD)/ In vivo xenograft model/ Clinical correlation	High	Yes	[127]
10	Oxaliplatin	circPDE4D▲	Tumor tissues, multiple CRC and resistant cell lines	miR-569/SP11	Promotes OXA sensitivity	In vitro functional assays (KD)/ Clinical correlation	Medium	Yes	[71]
11	Oxaliplatin	circHIPK3▲	49 tumor tissues, BALB/c nude mice, HT29, HCT116, and HEK293T cell lines	miR-637/STAT3/Bcl-2/ beclin1(Autophagy signaling pathway)	Promotes OXA resistance	In vitro functional assays (KD)/ In vivo xenograft model/ Clinical correlation	High	Yes	[128]
12	Oxaliplatin	circ_008218▲	24 sensitive vs. 24 resistant tissues, BALB/c nude mice NCM460, SW480 and HCT116 cell lines	miR-326/NFIB	Promotes OXA resistance	In vitro functional assays (KD)/ In vivo xenograft model/ Clinical correlation	High	Yes	[129]
13	Oxaliplatin	circ_0071589▲	40 paired tissues, BALB/c nude mice, Multiple CRC cell lines	miR-133b/SOX13	Promotes OXA resistance	In vitro functional assays (KD)/ In vivo xenograft model/ Clinical correlation	High	Yes	[130]
14	Oxaliplatin	circ_0079662▲	HT29, HCT116, HCT8 cell lines, nude mice	mir-324-5p/HOXA9 (TNF-α pathway)	Promotes OXA resistance	In vitro functional assays (KD)/ In vivo xenograft validation	High	Yes	[70]
15	Cetuximab	circ_0008274▲	11 sensitive vs. 4 resistant tissues, DiFi-R, and Caco-2-R cell lines	miR-140-3p/SMARCC1	Promotes CET resistance	In vitro functional assays (KD)/ Clinical correlation	Medium	Yes	[131]

Table 3 (continued)

No.	Drug	CircRNAs & Alteration	Model Systems	Target/pathway	Result	Key Validation Assays	Level of Evidence	In ceRNA Network?	ref
16	Cetuximab	circIFNGR2 ▲	Fresh tumor tissues, BALB/c athymic nude mice, extensive cell line panel	miR-30b/KRAS	Promotes CET resistance	In vitro functional assays (KD)/ In vivo xenograft model/ Clinical correlation	High	Yes	[132]
17	FOLFOX	circ_003283 ▲	50 FOLFOX treated tissues, 24 BALB/c nude mice, HCT116 resistant lines	miR-125-5p/MSI1	Promotes FOLFOX resistance	In vitro functional assays (KD)/ In vivo xenograft model/ Clinical correlation	High	Yes	[133]

Abbreviations: circRNA, circular RNA; 5-FU, 5-fluorouracil; OXA, Oxaliplatin; CET, Cetuximab; FOLFOX, Folinic acid, Fluorouracil, and Oxaliplatin; CRC, Colorectal Cancer; EMT, Epithelial-Mesenchymal Transition; OE, Overexpression; KD, Knockdown

Level of Evidence was defined as follows:

· High: In vitro functional assays (OE/KD) + in vivo xenograft validation with chemotherapeutic agent + clinical correlation

· Medium: In vitro functional assays with supporting clinical expression data or multi-model validation, but lacking in vivo drug response data

· Low: Primarily dysregulation data with preliminary functional validation in limited models (e.g., a single cell line), without strong clinical or in vivo correlation

phase, and reduced capabilities for both respiration and glycolysis [72].

These results strongly imply that *circHIF1A* mediates changes in HIF1α-driven glycometabolism, which contributes to cetuximab resistance in CRC.

CeRNAs networking regulate drug resistance in CRC

Profiles of lncRNAs, miRNAs, mRNAs, and ceRNA networks are closely related to chemoresistance, but in ceRNA regulatory circuits, different RNA species competitively bind shared miRNAs, thereby modulating the expression of drug-resistance related genes [73]. By sequestering miRNAs, ceRNAs can de-repress key targets involved in apoptosis, DNA repair, autophagy, and drug efflux, ultimately shifting the balance toward a chemoresistant phenotype. This competitive binding is influenced by ceRNA abundance, subcellular localization, miRNA binding-site affinity, and the stoichiometric ratio of miRNAs to ceRNAs factors that collectively determine the strength and direction of ceRNA-mediated regulation. For example, Yao et al. found that *LINC02418* functioned as an oncogenic lncRNA by acting as a ceRNA to sponge *hsa-miR-372-3p* and subsequently enhanced *EPHA2* expression. The LINC02418/miR-372-3p/EPHA2 axis contributes to 5-FU resistance in CRC and may represent a potential therapeutic target for improving CRC chemosensitivity [74].

CeRNAs related to 5-FU resistance

Numerous studies have been conducted to determine the effects of various lncRNAs and their interactions with other molecular components, such as miRNAs and genes, as well as their potential ceRNAs on 5-FU tumor resistance [75–78]. Among these, in a study conducted by Wu, Zou, et al., the interaction between *PCAT6* lncRNA, *HMGA2* mRNA, and *hsa-miR-204* was examined in vitro, concluding that these molecules form a ceRNA network that influences chemoresistance. Overall, the evaluation of 5-FU drug resistance indicated that numerous studies reported a significant ceRNA impact.

CeRNAs related to OXA resistance

Several efforts have been made to determine whether lncRNAs and other ceRNAs including miRNA and genes have a possible effect on OXA drug resistance. Concerning this area, a prominent study by Li et al. concluded that the downregulation of *KCNQ1OT1* lncRNA and the upregulation of *hsa-miR-34a* were associated with CRC resistance to OXA. The study evaluated the potential ceRNA elements, identifying *hsa-miR-34a* and *ATG4B* as the contributors to the ceRNA network [79].

CeRNAs related to bevacizumab resistance

Unfortunately, investigations on bevacizumab have not been done sufficiently but an example is represented by a novel ceRNA network consisting of *SNHG11* lncRNA, *hsa-miR-1207-5p*, and *ABCC1* gene that has been shown to increase resistance to bevacizumab both in in vitro and in vivo CRC models [80].

CeRNAs related to Cetuximab-Resistance

In light of the aforementioned reasons, studies have been conducted to investigate the effects of ceRNA network on cetuximab. For example, Gao, Hu et al. identified the upregulated *HCG18* lncRNA as a contributing factor in CRC cetuximab resistance, focusing on the miR-365a-3p/FOXO1/CSF-1 axis. Besides, the study examined the roles of the *FOXO1* gene and *hsa-miR-365a-3p*, as well as the ceRNA network involving these components. Consequently, the studied axis could illustrate a convincing ceRNA network that impacts the activity of cetuximab [81].

CeRNAs related to regorafenib resistance

Only one study was identified on the effect of the ceRNA network on CRC resistance to regorafenib. It was found that MIR570MG was upregulated and works as a molecular sponge for *hsa-miR-145*, whose levels were significantly reduced in resistant cells. This interaction resulted in the upregulation of *SMAD3*, a key signaling molecule that promotes survival and resistance mechanisms. These findings suggest that targeting the MIR570MG/miR-145/SMAD3 axis could provide new therapeutic strategies to overcome regorafenib resistance and potentially serve as biomarkers for treatment customization in CRC [82].

Non-coding RNAs evaluated in human clinical trials

To date, only microRNA-based therapeutics have reached human trials, such as the *miR-34a* mimic *MRX34* [83]. In contrast, no lncRNA- or circRNA-targeted approaches have progressed to clinical evaluation, largely due to delivery barriers and molecular complexity [84]. Advances in nanoparticle-based delivery systems may soon facilitate translation of these molecules into clinical applications.

Based on the relevance that ncRNAs, particularly miRNAs, may play in predicting responses to anticancer agents due to their high sensitivity and specificity at early time points, some clinical trials have been planned to elucidate such a potential role in patients. For example, MRX34, a liposomal mimic of the tumor-suppressive *hsa-miR-34a*, entered a phase I trial but was terminated due to severe immune-related toxicities, highlighting the need for improved delivery systems and comprehensive safety evaluations. Moreover, ongoing trials, such as NCT02466113, are exploring the use of a six-miRNA panel as a prognostic tool to guide adjuvant chemotherapy decisions in stage II colorectal cancer. Collectively, these studies underscore major challenges in the clinical translation of miRNA therapeutics, including targeted delivery, avoidance of off-target effects, immunogenicity, and assay standardization [83].

A clinical trial (NCT02466113, Registration Date: 2015-04-30), is investigating the opportunity to administer adjuvant chemotherapy in stage II colon cancer patients. The study, which began in 2016, is still ongoing. Researchers have developed a tool utilizing six miRNAs (*hsa-miR-21*, *hsa-miR-20a-5p*, *hsa-miR-103a-3p*, *hsa-miR-106b-5p*, *hsa-miR-143-5p*, and *hsa-miR-215*) to assist in determining whether a patient should receive chemotherapy or not. Patients are randomly assigned to two groups: one evaluated based on traditional pathological features (control group) and the other assessed using the miRNA tool (experimental group). The miRNA tool uses a specific risk score derived from the expression levels of the six miRNAs. Patients classified as high-risk by either method are recommended to undergo chemotherapy, while low-risk patients are monitored without additional treatment. The primary outcomes assessed are disease-free survival and overall survival.

On the other hand, a study analyzed the levels of 22 miRNAs and the Dicer protein in primary tumors from mCRC patients who were treated with capecitabine monotherapy [85]. Results showed that low expression of *hsa-miR-143* in primary tumors was associated with longer PFS. These findings suggest that *hsa-miR-143* could serve as a valuable biomarker for predicting sensitivity to fluoropyrimidines and warrant further investigation [85].

Given the limited treatment efficacy in CRC and the urgent need to address chemoresistance, it is crucial to identify and evaluate promising miRNA-based biomarkers through clinical trials. Moreover, considering the encouraging results of ncRNAs in overcoming drug resistance in CRC—some of which have already advanced to clinical trials—it is both necessary and highly beneficial to develop these molecules as reliable and effective biomarkers for detecting chemoresistance and improving treatment outcomes in CRC patients.

Limitations and future perspectives

Future progress in translating ncRNA-based strategies into clinical practice requires addressing several unresolved challenges, including the instability of RNA molecules, off-target effects, intratumoral heterogeneity, and the lack of efficient and tumor-specific delivery systems. These barriers explain why, despite compelling preclinical evidence, ncRNA-targeted therapeutics have not yet reached routine clinical use.

From our perspective, the most promising directions for drug development include chemically stabilized miRNA mimics, antisense oligonucleotides, circRNA-specific inhibitors, and advanced nanoparticle or lipid-based delivery platforms capable of targeted transport to colorectal tumors. Integrating high-throughput sequencing with liquid biopsy–based monitoring will further enhance real-time evaluation of treatment response and patient stratification.

Overall, incorporating ncRNA profiling into future clinical trials and developing clinically reliable delivery vectors represent the most impactful steps toward realizing personalized therapies for chemoresistant CRC patients.Future research should focus on validating ncRNAs as predictive biomarkers and therapeutic targets of chemoresistance in CRC. Large-scale transcriptomic and mechanistic studies are needed to define how specific miRNAs, lncRNAs, and circRNAs modulate pathways such as apoptosis, autophagy, and EMT.

Emerging data also indicate that ncRNAs influence immunotherapy response by regulating PD-L1, T-cell activity, and cytokine production within the tumor microenvironment, underscoring their potential as dual biomarkers for chemotherapy and immunotherapy resistance.

Despite promising evidence, clinical translation remains limited by delivery challenges and the lack of standardized validation. Combining high-throughput sequencing with liquid biopsy–based monitoring could improve real-time assessment of treatment response. Finally, integrating ncRNA profiling into future clinical trials may accelerate the development of personalized therapies for chemoresistant CRC patients.

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Declarations

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