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Lyu H, Chen JS, Tang JF, Zhou CF. miR-136: A biomarker in the inflammation-cancer transformation of gastric cancer. *World J Gastrointest Oncol* 2025; 17(12): 114173 [DOI: [10.4251/wjgo.v17.i12.114173](https://doi.org/10.4251/wjgo.v17.i12.114173)]

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## Molecular mechanism of non-coding RNAs-mediated radiosensitivity regulation in colorectal cancer

Xiao Li, Xiu-Xia Hao, Rui-Qing Zhu, Hong-Wei Zhou

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### Abstract

Colorectal cancer (CRC) remains a formidable global health challenge and is associated with dismal survival outcomes and high mortality among patients diagnosed at advanced stages. Despite advancements in early screening and therapeutic interventions, the outcomes of patients with advanced-stage CRC remain suboptimal, as these patients continue to exhibit a persistently low 5-year survival rate. Palliative radiotherapy (RT) is crucial for advanced CRC patients, but radioresistance remains a significant clinical challenge. This resistance is attributed to multiple mechanisms, such as genetic heterogeneity, dysregulated DNA damage repair and tumor microenvironment metabolic disorders. Recent studies have shown that noncoding RNAs (ncRNAs), mainly microRNAs, long ncRNAs (lncRNAs) and circular RNAs, play pivotal roles in regulating CRC radiosensitivity through diverse mechanisms, such as epithelial-mesenchymal transition, epigenetic reprogramming, posttranscriptional regulation and oncogenic signaling pathway activation. For example, microRNAs such as miR-141-3p and miR-630 enhance CRC radiosensitivity by targeting oncogenic pathways. In addition, lncRNAs, including the lncRNAs HOTAIR and LINC00630, influence the radiosensitivity of CRC through interactions with the DNA damage repair machinery and epigenetic modulators, respectively. In addition, circ\_0124554 acts as a competitive endogenous RNA to regulate oncogenic signaling. ncRNAs also serve as potential biomarkers for predicting radiosensitivity and prognosis. This review synthesizes the current evidence on the ncRNA-mediated regulatory networks that influence CRC radiosensitivity, emphasizing their potential as therapeutic targets to overcome RT resistance and improve outcomes in advanced CRC. By bridging mechanistic insights with clinical applications, this work aims

to guide future research and the implementation of precision RT strategies.

**Key Words:** Radiosensitivity; Noncoding RNAs; Colorectal cancer; Radiotherapy; Radioresistance

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**Core Tip:** Colorectal cancer (CRC), a leading cause of cancer mortality, shows less than 10% 5-year survival in advanced stages and radiotherapy is crucial for advanced CRC patients. Noncoding RNAs (ncRNAs), including microRNAs, long ncRNAs and circular RNAs, significantly influence CRC radiosensitivity through diverse mechanisms like epithelial-mesenchymal transition, epigenetic reprogramming, post-transcriptional regulation and oncogenic signaling pathways activation. They show promise as biomarkers for predicting radiosensitivity and prognosis, and as therapeutic targets to overcome radioresistance. Targeting ncRNA-mediated networks offers promising strategies to overcome radioresistance and improve outcomes, bridging molecular mechanisms with precision radiotherapy for advanced CRC.

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## INTRODUCTION

Colorectal cancer (CRC) ranks as the third most diagnosed malignancy globally, with more than 1.92 million (9.6%) new cases and 903859 (9.3%) deaths reported in 2022, making it the second leading cause of cancer-related mortality worldwide[1-3]. Advanced CRC has a dismal prognosis, with a 5-year survival rate of 10% for metastatic cases compared with 90% for localized disease[3]. Palliative radiotherapy (RT) constitutes a clinically validated intervention for patients with advanced CRC, demonstrating efficacy in achieving locoregional tumor control and mitigating disease-associated complications, including obstructive syndromes, hemorrhagic events, and refractory pain[4-6]. However, poor sensitivity to RT remains a critical barrier in the clinical management of CRC, with up to 30% of patients developing tumor recurrence due to intrinsic or acquired radioresistance, which is driven by genetic heterogeneity, dysregulation of DNA repair capacity, cell cycle regulation, and tumor microenvironment (TME) dynamics[7-12].

Noncoding RNAs (ncRNAs) are a diverse class of functionally active RNA molecules, including microRNAs (miRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs). These molecules orchestrate epigenetic reprogramming, signal transduction modulation, and posttranscriptional gene regulation[13-15]. Emerging evidence indicates that ncRNAs act as pivotal regulators of CRC radiosensitivity by controlling genomic stability maintenance, DNA damage repair (DDR), and cell cycle arrest[16-19]. For example, miRNAs regulate key oncogenic signaling pathways, such as the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) and Wnt/ $\beta$ -catenin pathways, which interact with radiation-induced DNA damage responses, ultimately determining CRC radiosensitivity[16]. Additionally, high LINC00630 expression in CRC not only correlates with radioresistance and poor prognosis but also directly drives therapeutic resistance. Knockdown of LINC00630 expression significantly increases CRC cell susceptibility to irradiation[20]. Similarly, circ-MFN2 promotes CRC radioresistance, proliferation, and metastasis by regulating the miR-574-3p/insulin-like growth factor 1 receptor (IGF1R) axis[21]. In this article, we review the ncRNA-mediated mechanisms that regulate radiosensitivity and propose potential clinical targets to improve the prognosis of advanced CRC.

## FUNCTIONS AND ROLES OF NCRNAS

On the basis of their structure and regulatory function, ncRNAs can be categorized into three main groups: lncRNAs (> 200 nt), miRNAs (18-22 nt), and circRNAs (covalently closed loops)[22,23]. MiRNAs bind to complementary sequences in the 3'-untranslated region of target mRNAs, leading to mRNA degradation or translational repression. For example, miR-21 promotes epithelial-mesenchymal transition (EMT) in Crohn's disease-associated intestinal fibrosis *via* the phosphatase and tensin homolog (PTEN)/mTOR axis[24]. lncRNAs can directly interact with the promoter regions of neighboring genes to modulate their transcriptional activity. Additionally, lncRNAs participate in posttranscriptional regulation by interacting with histone proteins, thereby altering the structure and state of chromatin[25]. CircRNAs play dual functional roles, acting as competitive endogenous RNAs (ceRNAs) or scaffolds for RNA-protein interactions. Their circular structure confers resistance to RNA exonucleases, enhancing their stability[26-28]. NcRNAs play important roles in cancer progression by regulating the TME, including immune regulation, signaling pathway regulation, and metabolic regulation[29]. For example, a myeloid-specific lncRNA from tumor-associated macrophages promotes aerobic glycolysis in breast cancer[30].

In CRC, ncRNAs drive proliferation and metastasis through EMT and epigenetic dysregulation[31]. Specifically, lncRNA H19 induces EMT in CRC cells *via* the miR-29b-3p/progranulin/Wnt axis, facilitating metastasis[32]. Furthermore, ncRNAs influence chemotherapeutic sensitivity by targeting drug resistance genes, positioning them as potential biomarkers or therapeutic targets[33]. For example, circRNA Protein disulfide isomerase family A member 3 (circPDIA3) interacts with the gasdermin E-C domain to enhance its autoinhibitory effect, thus suppressing pyroptosis. A positive feedback loop involving the circPDIA3/miR-449a/X-box binding protein 1 axis increases circPDIA3 expression, promoting chemoresistance[34]. These ncRNA-driven mechanisms underscore the dual utility of ncRNAs as diagnostic biomarkers and therapeutic targets in CRC. The role of ncRNAs in the occurrence and development of CRC has been systematically reviewed. In the following, we will mainly focus on the potential RT sensitization or resistance mechanisms of ncRNAs in the context of RT, and conduct a systematic review.

## MOLECULAR MECHANISM RESPONSIBLE FOR RADIOSENSITIVITY IN CRC

### DDR pathways

RT exerts its cytotoxic effects primarily by inducing DNA double-strand breaks, which are repaired through two major pathways: Nonhomologous end joining (NHEJ) and homologous recombination (HR)[35]. NHEJ operates throughout all cell cycle phases and is associated with high repair efficiency; however, it is prone to error, potentially exacerbating genomic instability[36]. Functional defects in NHEJ-associated genes (*e.g.*, *Ku70/Ku80* and DNA-dependent protein kinase catalytic subunit), such as *Ku70* protein depletion, markedly increase cellular radiosensitivity[37]. HR, a precise double-strand break repair mechanism active during the S and G2 phases, utilizes an intact sister chromatid as a template to restore DNA breaks with high fidelity, thereby maintaining genomic stability and preventing mutagenesis[38]. Notably, *BRCA1/BRCA2* mutations impair HR by disrupting RAD51-mediated DNA strand pairing, significantly increasing tumor cell sensitivity to RT[38,39]. In conclusion, compromised DNA repair machinery results in heightened vulnerability of tumors to radiation.

### Reduction-oxidation homeostasis regulation

Reduction-oxidation homeostasis plays a critical role in CRC radiosensitivity through the orchestration of metabolic adaptation and oxidative stress responses. Targeting these pathways may improve RT efficacy, as a dysregulated reduction-oxidation balance affects tumor radiosensitivity[40]. Tumor protein 53-induced glycolysis and apoptosis regulator suppresses glycolysis by reducing fructose-2,6-bisphosphate levels and diverting glucose flux toward nicotinamide adenine dinucleotide phosphate synthesis. This mechanism mitigates radiation-induced oxidative stress in tumors, as observed in gliomas[41,42]. Therapeutic targeting of tumor protein 53-induced glycolysis and apoptosis regulator disrupts metabolic reprogramming, increases reactive oxygen species accumulation, and amplifies DNA damage during RT, thereby enabling tumor radiosensitization[41]. Furthermore, epidermal growth factor receptor activation triggers Src family Fyn kinase-mediated tyrosine 481 phosphorylation of 6-phosphogluconate dehydrogenase. This modification potentiates nicotinamide adenine dinucleotide phosphate binding to increase 6-phosphogluconate dehydrogenase activity, which reduces reactive oxygen species levels, accelerates DNA replication, and decreases tumor radiosensitivity[43].

### Cell cycle checkpoints

The cell cycle is closely linked to tumor radiosensitivity, and the sensitivity of tumor cells to radiation varies markedly across distinct cell cycle phases[44]. RT activates DNA damage checkpoints, inducing multiphase cell cycle arrest (G1/S, S, and G2/M) to enable DNA repair or initiate apoptosis[45]. Key molecular pathways regulating the cell cycle include p53, cyclin G1, and checkpoint kinases 1/2, which coordinate checkpoint activation and repair mechanisms[11]. The tumor suppressor p53 critically enhances radiosensitivity at the G1/S checkpoint by inducing cell cycle arrest and apoptosis, thereby preventing damaged cells from progressing through replication[46]. Silencing cyclin G1 disrupts cell cycle progression and amplifies DNA damage accumulation, significantly increasing hepatocellular carcinoma radiosensitivity in preclinical models[47].

### Oncogene and tumor suppressor gene networks

Oncogenes and tumor suppressor gene networks regulate tumor radiosensitivity through EMT induction, which promotes therapeutic resistance[48]. The oncogene *NRP1* promotes radiation-induced EMT in lung adenocarcinoma *via* the transforming growth factor- $\beta$ 1/Smad2/3 signaling axis, upregulating critical EMT transcription factors such as SNAIL and TWIST[49]. Upregulation of pyruvate dehydrogenase kinase 1 expression activates the PI3K/AKT/mTOR pathway, which suppresses DDR mechanisms and reduces tumor radiosensitivity, promoting resistance to RT[50]. Pharmacological inhibition of pyruvate dehydrogenase kinase 1 enhances RT efficacy by restoring DNA repair capacity and overcoming PI3K/AKT/mTOR-driven resistance. Loss-of-function mutations in tumor suppressors, such as PTEN, disrupt apoptosis and differentiation pathways while simultaneously activating EMT programs that confer cancer stem-like properties and radiation resistance[51]. This dual regulatory role highlights EMT as a pivotal mechanism linking oncogenic signaling, tumor plasticity, and therapeutic resistance in radiation oncology.

### Epigenetic regulation

Epigenetic modifications, including DNA methylation and histone acetylation, dynamically regulate the transcriptional

activity of oncogenes (*e.g.*, *MYC*) and tumor suppressor genes (*e.g.*, tumor protein 53), thereby modulating tumor radiosensitivity. The RNA methyltransferase NOP2/Sun RNA methyltransferase family member 6 catalyzes m5C modifications on N-myc downstream regulates gene-1 mRNA, stabilizing its transcript to suppress apoptosis and confer radioresistance in cervical cancer models[52]. In non-small cell lung cancer, MED13 L physically interacts with the histone acetyltransferase P300 to mediate chromatin remodeling. MED13 L knockdown diminishes P300 chromatin recruitment, attenuating genome-wide histone H3 on lysine 27 acetylation signaling and impairing P300-dependent acetylation. This epigenetic rewiring suppresses oncogene transcription (*e.g.*, epidermal growth factor receptor) and sensitizes tumors to RT[53].

## ROLES OF NCRNAS IN THE REGULATION OF CRC RADIOSENSITIVITY

### **Roles of miRNAs in the regulation of CRC radiosensitivity**

Accumulating evidence highlights the critical role of miRNAs in modulating the radiosensitivity of CRC, with numerous miRNAs acting as tumor suppressors to sensitize tumors to RT (Table 1). For instance, miR-141-3p directly targets the oncogenic lncRNA distal-less homeobox 6 antisense 1. As reported previously, distal-less homeobox 6 antisense 1 is a lncRNA featuring an oncogene[54]. Destabilizing its structure and promoting its degradation results in increased CRC radiosensitivity through the suppression of pro-survival signaling pathways[55]. MiR-630, which is regulated by cyclic AMP response element-binding protein, increases radiosensitivity by targeting BCL2-like 2, an antiapoptotic BCL-2 family member, and TP53 regulating kinase, a p53-regulating kinase, thereby impairing DNA repair and promoting apoptosis[56]. Samadi *et al*[57] reported that increased let-7e expression levels are associated with reduced insulin-like growth factor-1 receptor protein levels, resulting in cell cycle arrest in G1 phase. MiR-31 binds to the 3'-untranslated region of serine threonine kinase 40, a negative regulator of nuclear factor- $\kappa$ B signaling, to increase radiation-induced apoptosis and suppress tumor growth[58]. MiR-124 is expressed at low expression levels in CRC cell lines and clinical CRC tissues and increases the radiosensitivity of CRC by targeting paired-related homeobox 1[59,60]. In addition, miR-378a-5p, which is associated with radioresistance when expressed at low levels in CRC, increases radiosensitivity by targeting low density lipoprotein receptor related protein 8, a component of the Wnt/ $\beta$ -catenin signaling pathway, thereby inhibiting prosurvival pathways[61]. These miRNAs collectively contribute to the modulation of CRC radiosensitivity, representing potential therapeutic targets for improving treatment outcomes.

Conversely, several oncogenic miRNAs drive radiation resistance in CRC through diverse mechanisms. Zheng *et al*[62] reported that miR-183-5p suppresses the expression of the autophagy-related gene autophagy related 5, impairing radiation-induced autophagic cell death and correlating with poor prognosis. High miR-622 expression levels are sustained after RT, promoting radioresistance by enhancing DNA repair and survival pathways, and miR-622 overexpression is linked to aggressive CRC phenotypes[63]. Exosomal miR-93-5p, which is secreted by cancer-associated fibroblasts, downregulates the tumor suppressor forkhead box protein A1 while upregulating the expression of the pro-EMT factor transforming growth factor- $\beta$ 3, thereby promoting proliferation and reducing apoptosis[64]. Similarly, exosomal miR-19b activates the Wnt/ $\beta$ -catenin pathway by targeting negative regulators and promoting cancer stemness and radioresistance, and high miR-19b expression is associated with poor clinical outcomes[65]. Zheng *et al*[66] reported that miR-106b increases tumor-initiating cell capacity and radioresistance *via* the PTEN/PI3K/AKT pathway and suppression of the cell cycle inhibitor cyclin-dependent kinase inhibitor 1A (p21). Additionally, miR-29a directly binds to PTEN mRNA, downregulating its expression and activating PI3K/AKT signaling to drive survival and radioresistance [63]. Finally, miR-222 amplifies PI3K/AKT signaling by suppressing PTEN, thereby reducing radiation-induced apoptosis and exacerbating therapeutic resistance[67]. These oncogenic miRNAs are involved in critical pathways that could be targeted to overcome radioresistance in CRC.

Additionally, miRNAs exemplify the critical interplay between epigenetic regulation and the DDR machinery in modulating therapeutic responses. MiR-4274 and miR-130a play pivotal roles in regulating DDR and radiosensitivity in CRC. The deletion polymorphism rs1553867776 in miR-4274 downregulates the expression of peroxisomal biogenesis factor 5, a peroxisomal biogenesis factor that interacts with Ku70 to maintain genomic stability. Reduced peroxisomal biogenesis factor 5 levels impair DDR by disrupting Ku70-mediated DNA repair, thereby increasing CRC radiosensitivity. Moreover, miR-130a acts as a potent radiosensitizer by suppressing DDR through multiple prosurvival pathways, including those involved in oxidative stress resistance and antiapoptotic signaling[68,69].

Notably, miRNAs also drive EMT and TME reprogramming. MiR-130a, mentioned above, reverses EMT in CRC and subsequently inhibits cell invasion capacity after RT[69]. Similarly, miR-124 directly targets paired-related homeobox 1, a transcription factor that promotes EMT, to regulate CRC radiosensitivity[60]. MiR-1226-5p, which is upregulated in radioresistant CRC cells (*e.g.*, HCT116), promotes EMT by suppressing interferon regulatory factor 1, leading to increased expression of EMT markers (TWIST, SNAIL, and N-cadherin) and enhanced invasion. The circRNA circSLC43A1 acts as a sponge to sequester miR-1226-5p and thus represents a therapeutic target to counteract the effects of miR-1226-5p[70]. In summary, miRNAs have complex and diverse mechanisms of action in the regulation of CRC radiosensitivity and are expected to be potential therapeutic targets to improve the effect of RT in CRC.

### **Roles of lncRNAs in the regulation of CRC radiosensitivity**

Emerging evidence highlights the critical roles of lncRNAs in regulating CRC radiosensitivity through diverse molecular mechanisms (Table 2). Silencing lnc-RI suppresses proliferation and increases apoptosis and radiosensitivity by impairing NHEJ repair *via* interactions with miR-4727-5p and DNA ligase 4 mRNA[71]. HOX antisense intergenic RNA is a lncRNA, and its expression is significantly upregulated in a variety of cancers and is associated with poor prognosis[72-74].

**Table 1** Several microRNAs involved in radiosensitivity of colorectal cancer

MicroRNAs	Target	Radiosensitivity	Ref.
miR-141-3p	DLX6-AS1	Increase	[55]
miR-630	BCL2 L2	Increase	[56]
let-7e	IGF-1R	Increase	[57]
miR-31	STK40	Increase	[58]
miR-124	PRRX1	Increase	[59,60]
miR-378a-5p	LRP8	Increase	[61]
miR-183-5p	ATG5	Decrease	[62]
miR-622	RB1	Decrease	[63]
miR-29a	PTEN	Decrease	[63]
miR-93-5p	FOXA1	Decrease	[64]
miR-19b	FBXW7	Decrease	[65]
miR-106b	PTEN and p21	Decrease	[66]
miR-222	PTEN	Decrease	[67]
miR-4274	PEX5	Increase	[68]
miR-130a	SOX4	Increase	[69]
miR-1226-5p	IRF1	Decrease	[70]

DLX6-AS1: Distal-less homeobox 6 antisense 1; BCL2 L2: BCL2-like 2; IGF-1R: Insulin-like growth factor-1 receptor; STK40: Serine threonine kinase 40; PRRX1: Paired-related homeobox 1; LRP8: Low density lipoprotein receptor related protein 8; ATG5: Autophagy related 5; RB1: RB transcriptional corepressor 1; PTEN: Phosphatase and tensin homolog; FOXA1: Forkhead box protein A1; FBXW7: F-box and WD repeat domain-containing protein 7; p21: Cyclin-dependent kinase inhibitor 1A; PEX5: Peroxisomal biogenesis factor 5; SOX4: SRY-related high-mobility-group box 4; IRF1: Interferon regulatory factor 1.

Similarly, HOX antisense intergenic RNA, which is overexpressed in CRC, drives radioresistance by stabilizing the ataxia-telangiectasia-mutated and Rad3-related protein-ATR-interacting protein complex to sustain DDR and by sponging miR-93 to upregulate the expression of the autophagy-related protein autophagy-related protein 12[75-77]. Another lncRNA, MALAT1, forms a feedback loop with ankyrin repeat and KH domain containing 1 (ANKHD1) and yes-associated protein 1 (YAP1) to amplify YAP1/AKT-mediated DDR, promoting therapeutic resistance[78]. As reported previously, the expression of ANKHD1, an oncogene, is upregulated in CRC and is correlated with YAP1 expression, and knock-down of ANKHD1 increases radiosensitivity in CRC, impairing DDR[79,80].

LncRNAs also act as ceRNAs to sponge specific miRNAs and regulate the expression of downstream target proteins, thus affecting the radiosensitivity of tumor cells. TTN-AS1 exacerbates radioresistance through the miR-134-5p/PAK3 axis, dysregulating P21 and activating AKT/glycogen synthase kinase-3 $\beta$ / $\beta$ -catenin signaling, whereas OIP5-AS1 increases radiosensitivity by sponging miR-369-3p to upregulate dual-specificity tyrosine phosphorylation-regulated kinase 1A expression, suppressing clonogenic survival and promoting irradiation-induced apoptosis[81,82].

LINC00630 confers radioresistance *via* enhancer of zeste homolog 2-dependent epigenetic silencing of brain expressed X-linked 1, whereas OTUD6B-AS1 sensitizes CRC to radiation by stabilizing tripartite motif containing 16 mRNA *via* human antigen R binding, amplifying glutathione peroxidase 4-dependent ferroptosis[20,83]. Conversely, lincRNA-ROR promotes radioresistance by suppressing the p53/miR-145 pathway, and reduced lincRNA-p21 expression is correlated with  $\beta$ -catenin-driven radioresistance[84,85]. SP100-AS1 promotes radioresistance through dual autophagy regulation: Stabilizing the autophagy-related gene 3 protein *via* ubiquitin-proteasome inhibition and sponging miR-622 to maintain autophagy-related gene 3 mRNA levels[86]. LncRNA UCA1 exacerbates resistance by suppressing apoptosis, prolonging G2/M arrest, and inducing EMT after radiation, whereas IGFL2-AS1 drives AKT pathway activation to increase survival [87,88]. These findings collectively indicate that lncRNAs are pivotal regulators of the response of CRC to radiation and offer promising therapeutic targets to overcome treatment resistance through the modulation of DDR, miRNA networks, epigenetic reprogramming, and critical signaling pathways.

### Roles of circRNAs in the regulation of CRC radiosensitivity

CircRNAs also play crucial roles in modulating CRC radiosensitivity through miRNA sponging and oncogenic signaling (Table 3). Zhong *et al*[89] reported that circ\_0124554 is upregulated in CRC and that its knockdown suppresses proliferation, migration, invasion, and tumor growth while increasing apoptosis and radiosensitivity. Mechanistically, circ\_0124554 sponges miR-1184 to derepress LIM and SH3 protein 1, a protumorigenic factor stabilized by methyltransferase-like 3-mediated N6-methyladenosine (m6A) methylation. Similarly, Zhang *et al*[90] reported that the overex-

**Table 2 Several long noncoding RNAs involved in radiosensitivity of colorectal cancer**

LncRNAs	Target	Radiosensitivity	Ref.
LINC00630	BEX1	Decrease	[20]
lnc-RI	miR-4727-5p and LIG4	Decrease	[71]
HOTAIR	miR-93 and ATR	Decrease	[75-77]
MALAT1	YAP1	Decrease	[78]
TTN-AS1	miR-134-5p	Decrease	[81]
OIP5-AS1	miR-369-3p	Increase	[82]
OTUD6B-AS1	HuR	Increase	[83]
LincRNA-ROR	miR-145	Decrease	[84]
LincRNA-p21	Wnt/ $\beta$ -catenin	Increase	[85]
SP100-AS1	miR-622	Decrease	[86]
UCA1		Decrease	[87]
IGFL2-AS1	AKT pathway	Decrease	[88]

LncRNAs: Long noncoding RNAs; BEX1: Brain expressed X-linked 1; LIG4: DNA ligase 4; ATR: Ataxia-telangiectasia-mutated and Rad3-related protein; YAP1: Yes-associated protein 1; HuR: Human antigen R; AKT: Protein kinase B.

**Table 3 Several circular RNAs involved in radiosensitivity of colorectal cancer**

CircRNAs	Target	Radiosensitivity	Ref.
circ-MFN2	miR-574-3p	Decrease	[21]
circ_0124554	miR-1184	Decrease	[89]
circ_0006174	miR-940	Decrease	[90]
circBANP	miR-338-3p	Decrease	[91]
circ_0055625	miR-338-3p	Decrease	[92]
circRNA CBL.11	miR-6778-5p	Decrease	[93]
circCCDC66	miR-338-3p	Decrease	[94]
circ_0067835	miR-296-5p	Decrease	[95]
circAFF2	CAND1	Increase	[97]

CircRNAs: Circular RNAs; CAND1: Cullin-associated and neddylation dissociated 1.

pression of circ\_0006174, along with that of IGF1R, is correlated with CRC progression. Silencing circ\_0006174 acts as a ceRNA to sequester miR-940, thereby increasing IGF1R-mediated survival signaling and radioresistance. Xie *et al*[91] demonstrated that the upregulation of circBANP expression in CRC increases radioresistance by sponging miR-338-3p and that silencing circBANP reverses these effects both *in vitro* and *in vivo*. Notably, Gao *et al*[92] revealed that circ\_0055625, which is overexpressed in colon cancer, sponges miR-338-3p to upregulate Musashi-1 (MSI1), promoting tumor progression and radioresistance. Depleting circ\_0055625 or MSI1 suppresses malignant phenotypes and increases radiosensitivity.

Furthermore, irradiation up-regulates circRNA CBL.11 in CRC cells, which acts as a ceRNA to sponge miR-6778-5p, restoring YWHAE and restraining proliferation[93]. Similarly, circCCDC66 is also significantly upregulated in CRC cells after irradiation, and knockdown of circCCDC66 reduces the cell viability of colon cancer cells under irradiation[94]. It is found that exosomal circ\_0067835 is significantly upregulated in the serum of CRC patients after RT, and knockdown of circ\_0067835 inhibits the progression of CRC and enhances the radiosensitivity of CRC cells *via* miR-296-5p/IGF1R axis [95].

Notably, m6A plays an important regulatory role in the occurrence and development of CRC, as well as radiosensitivity of CRC[96]. For example, circAFF2, a novel m6A-modified circRNA, enhances the radiosensitivity of CRC cells both *in vitro* and *in vivo*[97]. These studies collectively establish circRNAs (*e.g.*, circ\_0124554, circ\_0006174, circBANP, circ\_0055625, circRNA CBL.11, circCCDC66 and circ\_0067835) as critical regulators of CRC radioresistance *via* the miRNA-mediated derepression of oncogenic targets (LIM and SH3 protein 1, IGF1R, and MSI1). Their interplay with

epitranscriptomic modifiers such as methyltransferase-like 3 underscores their potential as therapeutic targets to enhance the efficacy of radiation in CRC.

## CLINICAL APPLICATION OF NCRNAS REGARDING THE SENSITIVITY OF CRC TO RT

### **NcRNAs as novel biomarkers for radiosensitivity**

Identifying biomarkers to predict CRC radiosensitivity is critical for personalized therapy. Afshar *et al*[98] revealed that when overexpressed, miR-185 sensitizes CRC cells to radiation by targeting IGF1R and IGF2, key regulators of survival pathways, positioning miR-185 as a predictive biomarker for CRC radiosensitivity. Khoshinani *et al*[67] reported that the oncogenic miRNAs miR-222 and miR-155 are markedly upregulated in radioresistant CRC cells produced using fractional X-ray irradiation. These miRNAs drive resistance by suppressing the expression of PTEN (miR-222) and forkhead box O3a (miR-155), highlighting their mechanistic roles in CRC radioresistance[67]. Liao *et al*[99] constructed a CRC miRNA-mRNA network (2275 miRNAs, 7045 targets) using the random walk with restart algorithm, revealing that miR-140-5p levels are elevated in radiosensitive patients and identifying it as a top candidate for predicting responses. Xu *et al*[100] reported that the expression of the lncRNAs NR\_015441 and NR\_033374 is positively correlated with radioresistance ( $P < 0.01$ ) in five CRC cell lines, suggesting the role of these lncRNAs as resistance biomarkers[100]. Collectively, these findings indicate that dysregulated ncRNAs, including miRNAs (miR-185, miR-222, miR-155, miR-506-3p, and miR-140-5p) and lncRNAs (R05532, NR\_015441, and NR\_033374), are promising tools for stratifying CRC patients and optimizing RT outcomes.

### **NcRNAs as novel potential prognostic biomarkers for RT efficacy**

NcRNAs have shown promise as prognostic biomarkers for predicting RT efficacy in CRC. Pathak *et al*[101] measured miR-652 expression in CRC patients with or without RT exposure *via* quantitative polymerase chain reaction and found that miR-652 was significantly downregulated in RT-treated cohorts. Notably, elevated miR-652 expression levels in RT-naive patients independently predicted reduced disease-free survival (hazard ratio = 7.398, 95% confidence interval: 0.217-3.786;  $P = 0.028$ ), positioning miR-652 as a biomarker for stratifying high-risk subsets for RT intensification. Similarly, miR-451a acts as a predictor of radiosensitivity due to its ability to regulate the expression of EMSY and CAB39, two targets linked to poor CRC prognosis. Low miR-451a expression is correlated with a poor RT response, suggesting its utility in identifying patients with limited therapeutic benefit[102]. Additionally, pretreatment miR-15b levels are positively associated with radiotherapeutic outcomes, with higher expression correlated with improved tumor regression grade and clinical benefits after neoadjuvant RT, highlighting its prognostic value[103]. Collectively, these findings highlight the potential of ncRNAs in predicting CRC RT efficacy and guiding personalized therapeutic strategies.

### **NcRNAs as novel potential RT targets for CRC**

Zhu *et al*[104] demonstrated that miR-145 suppresses stemness-associated transcription factors (*e.g.*, octamer binding transcription factor 4) and EMT, positioning it as a dual regulator of pluripotency and metastatic reprogramming. The overexpression of miR-145 increases CRC radiosensitivity by inhibiting the expression of snail family transcriptional repressor 1, a key EMT driver, suggesting that the snail family transcriptional repressor 1/miR-145 axis is a therapeutic target to reverse radioresistance through the concurrent suppression of EMT and cancer stem cell (CSC) plasticity. Despite the established role of EMT in therapeutic resistance and CSC maintenance, targeting EMT pathways remains challenging because of their complexity and dynamic interplay with CSCs. Khalighfard *et al*[105] analyzed plasma miRNA/mRNA profiles in CRC patients who received 30 sessions of RT and found that miR-101-3p, miR-145-5p, miR-26a-5p, and miR-34a-5p were upregulated and that miR-221-3p and miR-17-5p were downregulated; this indicates that these miRNAs are potential tumor suppressors with diagnostic and predictive value in CRC[105]. Collectively, these findings suggest that miRNAs such as miR-145 and miR-101-3p are critical regulators of EMT, CSCs, and the radiation response, representing actionable targets to overcome radioresistance.

## CHALLENGES AND FUTURE DEVELOPMENT

In addition to miRNAs, lncRNAs and circRNAs, small nucleolar RNAs are key regulators of CRC radiosensitivity. SNORA28 promotes the acetylation of histone H3 lysine 9 at the leukemia inhibitory factor receptor promoter and activates the leukemia inhibitory factor receptor/Janus kinase 1/signal transducer and activator of transcription 3 signaling axis by recruiting bromodomain-containing protein 4, thereby reducing the radiosensitivity of CRC[106]. Understanding these mechanisms may aid in the development of personalized RT strategies, maximizing efficacy and minimizing toxicity and resistance in CRC treatment.

Key challenges in targeting ncRNAs to increase CRC radiosensitivity include their complex mechanistic roles in DNA repair, apoptosis, and metabolic pathways, complicating the identification of dominant targets (*e.g.*, signal transducer and activator or ribosomal RNA modification). Clinical translation of ncRNA biomarkers (*e.g.*, small nucleolar RNA/LncRNA panels) is hindered by limited validation in liquid biopsies for distinguishing radiation-resistant subtypes. Functional redundancy among ncRNA classes (*e.g.*, lncRNA-circRNA sponging) and delivery challenges (*e.g.*, tumor-specific nanoparticle targeting) further impede therapeutic precision.

In the near future, it will be important to emphasize the ability to integrative multiomics approaches, such as single-cell transcriptomics and spatial proteomics, to decipher dynamic ncRNA networks in radiation-induced immune evasion or ferroptosis. Precision therapies could involve the combination of ncRNA modulation and radiosensitizers to disrupt metabolic adaptations such as glutamine dependency or target ncRNA-immune checkpoint crosstalk, such as that involving lncRNA-programmed death ligand 1. Artificial intelligence-driven predictive frameworks trained on multi-RNA profiles may refine patient stratification for personalized RT. Cross-cancer insights, leveraging conserved ncRNA pathways, could accelerate CRC-specific discoveries. These efforts aim to bridge mechanistic complexity with clinical translation, advancing ncRNA-targeted therapies to increase radiosensitivity and overcome radioresistance.

## CONCLUSION

In the field of CRC research, ongoing investigations into ncRNAs are providing valuable insights for improving RT outcomes. To date, findings indicate that ncRNAs, such as miRNAs, lncRNAs, and circRNAs, significantly influence CRC radiosensitivity through diverse mechanisms, including epigenetic reprogramming and posttranscriptional regulation. These molecules can either increase or reduce radiosensitivity, resulting in a complex regulatory landscape. Clinically, ncRNAs show promise as biomarkers for predicting radiosensitivity and prognosis and as potential therapeutic targets to overcome radioresistance. However, challenges persist in fully harnessing their potential. Future research should focus on multiomics integration to better understand ncRNA networks, develop precision combination therapies, utilize Artificial intelligence-driven models for patient stratification, and draw on cross-cancer insights to accelerate CRC-specific discoveries. Addressing these challenges and exploring innovative strategies will be crucial for translating ncRNA research into clinical applications, ultimately enhancing personalized RT approaches and improving the outcomes of advanced CRC patients.

## FOOTNOTES

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