Curcumin Targeting Non-Coding RNAs in Colorectal Cancer

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Colorectal cancer is one of the most common gastrointestinal malignancies, with high incidence rates, a low rate of early diagnosis, and complex pathogenesis. In recent years, there has been progress made in its diagnosis and treatment methods, but tumor malignant proliferation and metastasis after treatment still seriously affect the survival and prognosis of patients. Therefore, it is an extremely urgent task of current medicine to find new anti-tumor drugs with high efficiency and safety and low toxicity. Curcumin has shown potent anti-tumor and anti-inflammatory effects and is considered a hot spot in the research and development of anti-tumor drugs due to its advantages of precise efficacy, lower toxic side effects, and less drug resistance. Recent studies have revealed that curcumin has anti-tumor effects exerted on the epigenetic regulation of tumor-promoting/tumor-suppressing gene expression through the alteration of expression levels of non-coding RNAs (e.g., lncRNAs, miRNAs, and circRNAs). The interaction between curcumin and non-coding RNAs on the occurrence and development of colorectal cancer is summarized herein.

curcumin colorectal cancer non-coding RNAs epigenetic regulation anti-tumor

1. Introduction

Colorectal cancer (CRC) ranks third in the incidence of malignant tumors and is the second leading cause of cancer-related death worldwide [1][2]. According to the global cancer statistics issued by International Agency for Research on Cancer (IARC), 1.9 million new cases (third highest incidence) and 935,000 colorectal cancer deaths (second highest mortality) were estimated to have occurred worldwide in 2020 [3] . The global burden of colorectal cancer is expected to be more than 2.2 million new cases a year and 1.1 million deaths in 2030 [4]. In China, the incidence and mortality of colorectal cancer have also increased due to variations in diet and the population age structure [5][6]. Due to the lack of early specific warning signs of colorectal cancer, most patients are in phases III and IV at the first visit and might lose the opportunity to receive effective standard treatment, resulting in a 5-year survival rate of 40% [7][8]. Therefore, it is urgent to find new therapeutic methods and develop effective biomarkers for the early diagnosis, treatment, and prognosis assessment of colorectal cancer to improve the survival status. Some studies have demonstrated that epigenetic mechanisms play a key role in cancer progression, particularly non-coding RNAs (ncRNAs) [9]. Indeed, many studies have demonstrated that the development pathogenesis of colorectal cancer is highly influenced by ncRNAs [10], the abnormal expression of oncogenic and tumor-suppressor molecules, and the abnormal activation of various cell signaling pathways [11][12]. In recent years, some important natural compounds, such as phenolics, terpenoids, and meroterpenoids, have been confirmed to have anticancer

effects by regulating the expression and function of ncRNAs [13]. Particularly, naturally derived polyphenols have been safely used for many years and have shown real potential for therapeutic effects in most cancers through the regulation of miRNAs and lncRNAs [14][15][16]. The initial epigenetic changes associated with cancer may be regulated by many polyphenols [17][18][19], such as curcumin [20][21], resveratrol [22][23], and so on. Among them, curcumin, with the advantages of less toxicity and less side effects, has been clarified to be an effective compound in the treatment of colorectal cancer. Therefore, summarizing the scientific progress of curcumin targeting ncRNAs in colorectal cancer and understanding the inducement and molecular regulatory mechanisms of colorectal cancer is essential in finding key targets for clinical treatment and will also provide theoretical guidance for basic research, clinical drug selection, and gene therapy.

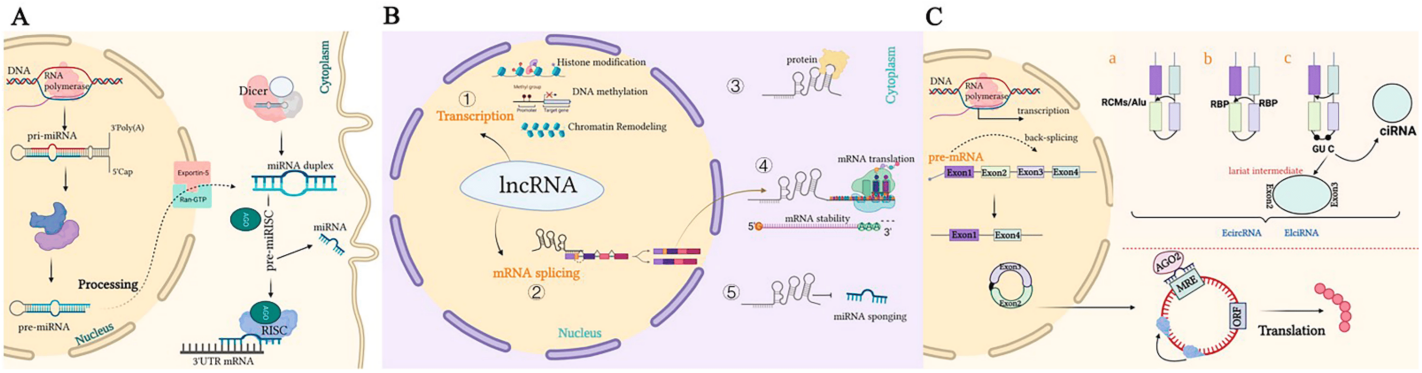

Figure 1. Representation of the biogenesis and mode of action of ncRNAs. (**A**). A pri-miRNA with a double-stranded stem-loop is formed after transcription, which is cleaved by Drosha and DGCR8 with a hairpin-based secondary structure; two nucleotides overhang at its 3′ end. Then, pre-miRNAs are exported to the cytoplasm by exportin-5/Ran-GTP. Here, pre-miRNA forms a mature double-stranded miRNA duplex digested by Dicer. The miRISC complex formed by the guide strand miRNA and Ago protein represses target mRNAs by base-pairing at 3'UTR, which prevents translation and selectively silences gene expression. (**B**). Mechanisms underlying long non-coding RNA (lncRNA)-mediated regulation of gene expression. ① Transcription regulation by lncRNAs. ② lncRNAs are engaged in the processing and maturation of mRNAs ③ lncRNAs interact with proteins. ④ lncRNAs interact with RNAs. ⑤ lncRNAs can competitively bind to miRNAs by acting as ceRNAs, thereby blocking the inhibition of the target gene. (**C**). Biogenesis of circRNAs. a. The back-splicing circularization requires the help of complementary sequences (ALU repeats and RCMs). b. RBP-mediated circularization. c. Lariat-driven circularization. circRNA can serve as a miRNA sponge, which inhibits miRNAs in order to regulate the expression of target genes or interact with proteins.

2. Curcumin and Colorectal Cancer Therapy Based on Non-Coding RNAs' Epigenetic Regulation

2.1. Curcumin Against Colorectal Cancer Mediated by miRNAs

Many studies have demonstrated that the occurrence, development, treatment, and prognosis of colorectal cancer are all involved with miRNAs in varying degrees [24][25]. miRNAs can regulate the expression of their target

oncogenes or cancer suppressor genes to affect the various biological processes of cancer, including cell proliferation, apoptosis, cell cycle, and metastases, in the occurrence and development of malignant tumors [26]. Some studies have indicated that curcumin could exert anti-colorectal cancer effects by targeting differentially expressed miRNAs [27][28]. The miRNAs regulated by curcumin in colorectal cancer are summarized in Table 1.

Table 1. Curcumin modulates miRNAs in colorectal cancer.

In Vitro/ In Vivo	Cell Line	Modulated by Curcumin	Target Gene	Relevant Mechanism	Biological Effects After Administration	Refs
In vitro/ in vivo	Rko, HCT116, HT-29, SW620	miR-21 ↓ miR-21-3p, miR-21-5p ↓	PDCD4 PTEN ATG10, APAF1	Suppress AP-1 binding to the promoter, p-Akt	Inhibits tumor growth, migration, invasion, metastasis. Promotes autophagy, apoptosis	[29] [30]
In vitro	SW480	miR-130a ↓	—	Wnt/β-catenin pathway	Inhibits proliferation	[31]
In vitro/ in vivo	HCT116, SW480, HCT116p53$^{-/-}$	miR-34a ↑ miR-27a ↓	CDK4, CDK6, cMyc, FBXW7, Cyclin D1	Deregulation of miRNAs —	Inhibits proliferation, tumor growth, chemoresistant. Promotes cell cycle arrest, apoptosis	[32]
In vitro	HCT-116	miR-491 ↑	PEG10	Wnt/β-catenin pathway	Inhibits proliferation and promotes apoptosis	[33]
In vitro	HCT116−5FUR, SW480-5FUR	miR-141, miR-101, miR-	—	—	Inhibits EMT	[34]

		200b, miR-429, miR-200c ↑	ZEB1 BMI1			
In vitro	HCT-116, L-OHP	miR-409-3p ↑	ERCC1	—	Inhibits migration and invasion; promotes apoptosis.	[35]
In vitro	RKO, SW480	miR-20a, miR-27a, miR-17 ↓	ZBTB4, ZBTB10, Sp1, Sp3, Sp4,	—	Inhibits proliferation	[36]
In vitro/in vivo	SW620, HCT116, HCT116wt, HCT116 $p53^{-/-}$	miR-34a ↑ miR-34c ↑	Notch-1	—	Inhibits proliferation, promotes apoptosis	[37]
In vitro/in vivo	SW480	miR-145 ↑ (Nano-CUR)	—	—	Interferes with tumor growth, inhibits proliferation, migration	[38]
In vitro/in vivo	HCT116, LoVo, HT29-MTX	miR-31 (PS-TP-miR-31i/Cur NPs)	—	—	Inhibits cell proliferation, tumor growth	[39]
In vitro	HT-29, HCT-116, LoVo, SW480, DLD-1 CRL-1790	miR-137 ↓	GLS	GLS–gluamine Metabolism	Increases cell death, anti-chemoresistance	[40]
In vitro	HT-29	miR-21, miR-155,	—	—	Promotes apoptosis	[41]

		miR221/222 ↓ miR-34a, miR-126 ↑				

Note: Arrows "↓, ↑" represent the expression levels of miRNAs regulated by curcumin in CRC. "↑": upregulate "↓" : downregulate

2.2. Curcumin against Colorectal Cancer Mediated by LncRNAs

LncRNAs, as effective marker molecules, have been used in the diagnosis and prognosis of many cancers. The abnormal expression of some lncRNAs is involved in various processes, such as regulating the growth and metastasis of tumor cells [42]. Curcumin could significantly change the proliferation, migration, and invasion of colorectal cancer cells by regulating lncRNAs [43]. Furthermore, the mechanism of lncRNAs that interact with curcumin to moderate signal transduction needs to be further explored. Therefore, this section will discuss the intervention effect between curcumin and lncRNAs in colorectal cancer and its anti-colorectal cancer mechanism. The above-mentioned results have gradually provided new evidence for the basic research of lncRNAs combined with curcumin for the treatment of colorectal cancer. The data are shown in Table 2.

Table 2. Curcumin modulates lncRNAs in colorectal cancer.

In Vitro/ In Vivo	Cell Line	Modulated by Curcumin	Relevant Mechanism	Biological Effects after Administration	Refs
In vitro	HCT116, SW480	NBR2 ↑	Activates of AMPK pathway	Inhibits proliferation	[44]
In vitro/ In vivo	HCT8 DDP cells	KCNQ1OT1 ↓	Sponge of miR-497 increases Bcl-2 expression	Inhibits proliferation, promotes apoptosis, chemoresistant	[45]
In vitro	DLD-1, SW620, HCT116	PANDAR ↓	PUMA upregulation	Promotes apoptosis	[46]
In vitro/ In vivo	DLD-1	PANDAR ↓	Induces PUMA	Promotes apoptosis, reduces cell aging	
In vitro	SW480	MALAT1 ↓ (Si-MALAT1)	Downregulated c-myc, cyclinD1, β-catenin	Inhibits cell viability, migration, invasion	[47]
In vitro/ In vivo	HT-29	CCAT1 ↓ (Si-CCAT1-CSNP)	—	Inhibits proliferation, migration, induces apoptosis	[48]

Note: Arrows "↓, ↑" represent the expression levels of lncRNAs regulated by curcumin in CRC. "↑ : upregulate "↓" : downregulate

2.3. Curcumin and Anti-tumor Effect Mediated by CircRNAs

circRNAs have great potential research value in the occurrence, development, diagnosis, prognosis, and treatment of tumors. Recent studies have revealed that phytochemicals such as curcumin could further exert anti-tumor effects by regulating circRNAs that are engaged in biological processes, including tumor cell proliferation, apoptosis, migration, invasion, autophagy, chemosensitivity, and radiosensitivity [49]. Considering the pivotal roles of circRNAs combined with drugs in cancer, researchers found that curcumin could regulate the occurrence and

development of various tumors through circRNAs acting on different signaling pathways. The research results of the role of circRNAs in various tumors under the action of curcumin in the past 12 years are summarized in Table 3.

Table 3. Curcumin modulates circRNAs in various cancers.

In Vitro/ In Vivo	Cell Line	Modulated by Curcumin	Relevant Mechanism	Biological Effects after Administration	Refs
In vitro/ In vivo	H1650, H1299, H460, A549, 16HBE (NSCLC)	circ-PRKCA ↓	circ-PRKCA/miR-384/ITGB1 pathway	Inhibits viability, colony formation, migration, invasion, promotes apoptosis	[50]
In vitro/ In vivo	THLE-2, HuH-7, HCCLM3 (HCC)	circ-ZNF83 ↓	JAK2/STAT3 pathway circZNF83/miR-324-5p/CDK16 axis	Inhibits proliferation, cell cycle, migration, invasion, promotes apoptosis	[51]
In vitro/ In vivo	SKOV3, A2780, IOSE-80 (Ovarian cancer)	circ-PLEKHM3 ↑	circ-PLEKHM3/miR-320a/SMG1 axis	Inhibits proliferation and promotes apoptosis	[52]
In vitro/ In vivo	CAKI-1, ACHN, (RCC)	circ-FNDC3B ↓	circ-FNDC3B/miR-138-5p/IGF2 axis	Inhibits proliferation, promotes apoptosis	[53]

In vitro	CNE-2 (NPC)	circRNA-102115	circRNA-102115/miR-335-3p/MAPK1	Enhances radiosensitization	[54]
In vitro	CNE-2 (NPC)	circRNA network	miRNA sponge regulated EGFR, STAT3, GRB2	Enhances radiosensitization	[55] [56]

Note: Arrows "↓, ↑" represent the expression levels of circRNAs regulated by curcumin in various cancers. "↑": upregulate "↓" : downregulate

Meanwhile, researchers found evidence for the potential role of some circRNAs as diagnostic markers for colorectal cancer, as shown in Table 4.

Table 4. Roles of circRNAs in colorectal cancer.

In Vitro/In Vivo	Cell Line	circRNAs in CRC	Target Gene	Relevant Mechanism	Biological Effects	Refs
In vitro/ In vivo	RKO, HCT116, SW480, SW620, DLD-1, HT29, Colo320, HCE8693	circ-RHOBTB3 ↓	PTBP1, FUS ADARB2	circ-RHOBTB3/HuR/PTBP1 protein ubiquitination	Restrains metastasis, invasion	[57]
In vitro/ In vivo	HCT116, SW480	circ-3823 ↑	TCF7	circ-3823/miR-30c-5p/TCF7 miRNA sponge m6A modification	Promotes proliferation, metastasis, angiogenesis	[58]

In vitro	FHC, HCT116, DLD1, LoVo, SW620, HT29, SW480	circ-IL4R ↑	PHLPP1	circ-IL4R/PI3K/AKT, miRNA sponge, protein ubiquitination	Promotes proliferation, migration, invasion	[59]
In vitro/ In vivo	HT-29, SW480, HCT-116, LoVo, NCM460	circ-N4BP2L2 ↑	CXCR4	circ-N4BP2L2/miR-340-5p/ CXCR4 (miRNA sponge)	Promotes proliferation, migration, invasion. Promotes tumor growth, metastasis	[60]
In vitro/ In vivo	HT290, HCT116, SW480, SW620, FHC	circ-CUL2 ↓	PPP6C	circ-CUL2/miR-208a-3p/PPP6C (miRNA sponge)	Inhibits proliferation ability, induces apoptosis, autophagy	[61]
In vitro/ In vivo	HT-29, LoVo, SW480, HCT-116, NCM460	circ-PTK2 ↑	YTHDF1	circ-PTK2/miR-136-5p/YTHDF1	Promotes proliferation, migration, invasion, chemoresistance	[62]

Note: Arrows "↓, ↑" represent the expression levels of circRNAs in CRC. "↑ : upregulate "↓" ：downregulate

Throughout the last decade of research, researchers have identified a series of circRNAs [63] as biomarkers of oncogenic/tumor-suppressive genes that exert anti-colorectal-cancer functions. Although the regulation of these functional molecules of circRNAs has gradually entered public view, the research on circRNAs has just begun. These circRNAs may provide new evidence for future research on the mechanism of colorectal cancer occurrence and development. Whether those circRNAs are responsible for the treatment of colorectal cancer and how circRNAs regulate the biological effects of tumor cells after the curcumin intervention have still not been studied. There is still plenty of room to explore the effect of curcumin on colorectal cancer through circRNAs.

3. Discussion

Curcumin can interact with multiple molecular targets through a variety of complex molecular mechanisms to inhibit the growth of tumor cells and achieve anti-colorectal-cancer and chemotherapy sensitization effects. Compared with traditional chemotherapy drugs, curcumin has higher safety levels and is widely used as an ingredient in dietary formulations for the prevention of colorectal cancer. Related clinical trials have been launched. The evidence listed above identifies the mechanism of ncRNAs as potential targets of curcumin for colorectal cancer treatment, summarized in Figure 2. As an explicit regulatory mechanism, miRNAs regulate target mRNAs through complete or incomplete base pairing with 3′UTRs **(Figure 2-ⅰ)**, lncRNAs interact with DNAs, RNAs, and proteins to regulate transcription and post-transcriptional processes **(Figure 2-ⅱ)**; circRNAs interact with proteins to regulate the alternative splicing and transcription of target genes **(Figure 2-ⅲ)**. In particular, current studies on ncRNAs regulated by curcumin have been mainly focused on the ceRNA mechanism, also known as the molecular sponge effect, which mainly involves the lncRNAs/circRNAs–miRNAs–mRNAs–proteins pathway. Briefly, target genes can be silenced by miRNA binding. However, ceRNAs, including lncRNAs and circRNAs, can regulate target gene expression by competitively absorbing miRNAs. The mutual regulation between these transcripts (mRNAs and ncRNAs) plays an important role in the occurrence and development of colorectal cancer and mediates biological processes, including colorectal cancer cell proliferation, apoptosis, metastasis, and chemoresistance **(Figure 2-ⅳ)**. As a new research tool or idea, ceRNAs have also been crossed, penetrated, and merged with research in drug-related fields, such as in research on curcumin. Researchers found that curcumin has shown a significant anti-tumor effect in the epigenetic regulation of ncRNAs according to the research progress in the past 12 years. Curcumin could affect the development of colorectal cancer by targeting oncogenes such as miR-130a/miR-137, miR-20a/miR-27a, miR-21, and miR-221/222 or tumor-suppressor genes such as miR-101/miR-409-3p, miR-200b/miR-200c, and miR-34a/miR-34c; its anti-colorectal cancer effect is essentially through the indirect regulation of target genes or signaling pathways. Treated by curcumin, Lnc NBR2, Lnc KCNQ1OT1, Lnc PANDAR, and Lnc CCAT1 could prove to be potentially effective target molecules in the treatment progress of colorectal cancer. Whether a large number of differentially expressed circRNAs, such as circ-3823, circ-IL4R, and circ-CUL2 in colorectal cancer, could become effective targets for curcumin in the treatment of colorectal cancer remains to be further clarified **(Figure 2-ⅴ)**. In summary, these findings could provide favorable evidence for exploring the role of curcumin in the treatment of colorectal cancer via non-coding RNAs, which may provide new directions for the treatment and prognosis of colorectal cancer patients. Non-coding RNAs can be potential therapeutic targets for the occurrence and development of colorectal cancer, and curcumin-targeted non-coding RNAs have good biomarker and reference significance for the treatment of colorectal cancer.

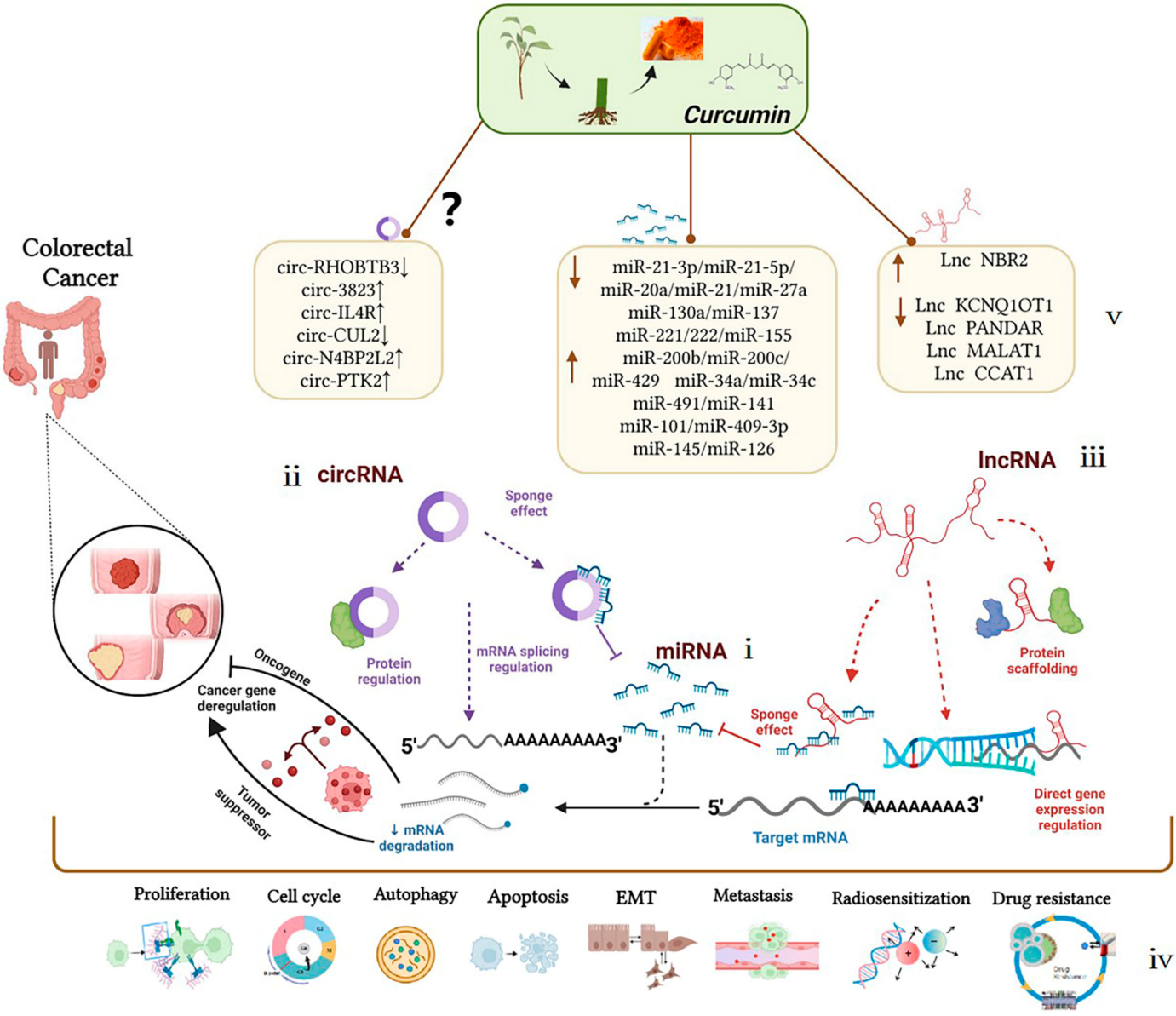

Figure 2. Mechanism of curcumin-targeted regulation of non-coding RNAs against colorectal cancer. Dotted lines represent different regulation methods; boxes represent different ncRNAs regulated by curcumin.

However, the efficacy, reliability, and sensitivity of ncRNAs as biomarkers and therapeutic targets for colorectal cancer need further basic research and clinical application. Although different types of ncRNAs have been identified to be involved in the curcumin treatment of colorectal cancer, the existing research has the following issues: (I) The regulation relationship between ncRNAs and curcumin can be found via gene knockdown and overexpression; however, whether this kind of relationship, which exists in a single cell, can be realized in the complex system of the human body still needs to be verified via further clinical trials. (II) Whether curcumin can inhibit the occurrence and development of colorectal cancer through the targeted and precise regulation of the copy number, subcellular localization, and protein binding ability of non-coding RNAs is worthy of further exploration. Additionally, the low stability, low oral bioavailability, and dose-dependent pharmacological effects of curcumin limit its clinical application in cancer therapy and industrialization. Nevertheless, curcumin is a potential candidate compound for anti-tumor drugs due to its clear biological activity and relatively simple molecular

structure. The development of a new and more efficient drug delivery system of curcumin will guide its significance in the research on targeting ncRNAs and provide a new prospect for human cancer treatment [64][65]. Therefore, for better detection and effective cancer treatment, molecular diagnostic methods combined with drug treatments such as curcumin need to be researched in-depth to enrich their significance and contribute to their clinical application.

Undeniably, more differentially expressed miRNAs, lncRNAs, and circRNAs associated with colorectal cancer need to be further explored. The researchers look forward to more studies on curcumin regulating ncRNAs in colorectal cancer.

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