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REVIEW
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The Relationship Between the Network of Non-coding RNAs-Molecular Targets and N6-Methyladenosine Modification in Colorectal Cancer

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Recent accumulating researches implicate that non-coding RNAs (ncRNAs) including microRNA (miRNA), circular RNA (circRNA), and long non-coding RNA (lncRNAs) play crucial roles in colorectal cancer (CRC) initiation and development. Notably, N6-methyladenosine (m^6A) methylation, the critical posttranscriptional modulators, exerts various functions in ncRNA metabolism such as stability and degradation. However, the interaction regulation network among ncRNAs and the interplay with m^6A-related regulators has not been well documented, particularly in CRC. Here, we summarize the interaction networks and sub-networks of ncRNAs in CRC based on a data-driven approach from the publications (IF > 6) in the last quinquennium (2016–2021). Further, we extend the regulatory pattern between the core m^6A regulators and m^6A-related ncRNAs in the context of CRC metastasis and progression. Thus, our review will highlight the clinical potential of ncRNAs and m^6A modifiers as promising biomarkers and therapeutic targets for improving the diagnostic precision and treatment of CRC.

Keywords: long non-coding RNA, micro RNA, interaction network, colorectal cancer, N6-methyladenosine modification

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INTRODUCTION

Background

Colorectal cancer (CRC) remains the third most common tumor worldwide with increasing incidence and mortality rates annually. The etiology of CRC is complicated and involves a variety of risk factors such as environmental exposure, genetic alterations as well as a variety of epigenetic modifications based on global molecular biomarkers such as mRNA, microRNA (miRNA), long non-coding RNA (lncRNA), circular RNA (circRNA), etc. Genomic studies show that human ncRNA transcripts that do not encode for proteins account for approximate 98% of the total human transcripts, which consist mainly of lncRNA, miRNA and circRNA, etc.

Among them, lncRNAs are non-coding RNAs longer than 200 nt, which play critical roles in regulating gene expression and chromatin dynamics (Bhan and Mandal, 2015). MiRNAs are ncRNAs with a length of 17–25 nt, which usually recognize the 3′UTR of mRNA and inhibit gene expression (Lee and Dutta, 2009). CircRNAs are single-stranded ncRNAs with a covalent closed loop structure, which play important biological functions by acting as miRNA inhibitors, protein "bait" or by encoding small peptides (Li et al., 2020). Notably, accumulating evidence shows that the dysregulated ncRNAs (such as lncRNAs, microRNAs, circRNAs, etc.) are involved in the pathological process of a variety of tumors such as prostate cancer, breast cancer, hepatic cancer, and CRC. Although several studies show that ncRNAs play critical regulatory roles in CRC by targeting different protein-coding transcripts or other ncRNAs to activate various signal pathways. However, the specific mechanism underlying the functions of ncRNAs in CRC remain unclear.

Accumulating researches show that ncRNAs are abnormally expressed in tissues, cells, exosomes, and blood of CRC patients (Barbagallo et al., 2018). These are identified as oncogenes or tumor suppressors that mediate CRC occurrence, metastasis, and resistance to radiotherapy and chemotherapy (Wang et al., 2017a; Luan et al., 2020; Meng et al., 2020). Although the regulatory mechanism of the biogenesis and function of ncRNAs remain unclear, existing studies show that ncRNAs play essential roles during tumorigenesis and progression through diverse mechanisms including action as miRNA sponges or baits, interaction with RNA binding proteins, translation to functional peptides as well as epigenetic modification mediated mechanisms (Ren et al., 2018a; Ni et al., 2019; Long et al., 2021). Notably, epigenetic modification of ncRNAs is a significant factor in the occurrence and development of CRC. Meanwhile, ncRNAs can also rely on epigenetic modification to regulate the expression of mRNA or ncRNAs and ultimately promote the progression of CRC. Among all epigenetic modifications, m^6A, as a research hotspot in recent years, exerted its critical functions in the progression and development of CRC. Specifically, the m^6A writers (METTL3, METTL14, WTAP, and other writers such as RBM15, VIRMA, CBLL1, ZC3H13) are responsible for "writing" m^6A modification. The m^6A erasers (FTO and ALKBH5) are responsible for "erasing" m^6A modification. Meanwhile, m^6A readers (YTHDC1-2, YTHDF1-3, IGF2BP1-3, HNRNPC and HNRNPA2B1) are responsible for "reading" m^6A modification. The writers, erasers and readers of m^6A modification can collaborate and directly participate in the progression of various types of tumors. In CRC, m^6A modification promotes CRC angiogenesis, metastasis, and chemical resistance by regulating lncRNA stability and degradation, miRNA biogenesis, and circRNA reverse splicing and translation (Dang et al., 2021; Liu et al., 2021; Xu et al., 2021). Recently, publications focused on that m^6A associated was supposed to regulate the expression of ncRNAs (Wu et al., 2019a; Chen et al., 2020a; Yang et al., 2020a). Yang et al. illustrated that knockdown of METTL14 enhanced the expression of long non-coding RNA XIST through YTHDF2 pathway (Yang et al., 2020a). Wu et al. clarified that m^6A-induced lncRNA RP11 triggered the metastasis of CRC cells through the post-translational up-regulation of Zeb1 (Wu et al., 2019a). Similarly, Peng et al. demonstrated that METTL14 promoted the expression of miR-375 in an m^6A-dependent pathway to promote the progression of CRC (Chen et al., 2020a). Furthermore, not only m^6A can regulate the expression of ncRNAs, ncRNAs are capable to regulate the m^6A level of RNA as well. For example, miR-96 downregulated AMPKα2, thereby blocking its m^6A modification and leading to increased FTO expression and subsequent upregulation of MYC expression (Yue et al., 2020); LNC00460 directly interacted with IGF2BP2 and DHX9 to bind to the 3′UTR of HMGA1 mRNA, thereby increasing the stability of HMGA1 mRNA (Hou et al., 2021); m^6A modified circNSUN2 stabilized HMGA2 mRNA and ultimately promoted liver metastasis of CRC by forming a circNSUN2/IGF2BP2/HMGA2 RNA-protein ternary complex. Thus, linking ncRNAs and m^6A modifications is essential for advancing future diagnostic and therapeutic inventions (Chen et al., 2019a). The correlation between ncRNAs and m^6A modification is shown in **Figure 1**.

The current researches on ncRNAs in CRC are limited on the selection of one or more representative ncRNAs in clinical genomics. In these studies, the CRC transcriptome is analyzed in cohort retrospectively and usually lacks a holistic approach. The current research is primarily based on miRNA as the representative of ncRNAs, which usually regulate biological functions and promote or inhibit the occurrence of tumors by affecting the expression of multiple direct or indirect targets in common biological networks. For each ncRNA, hundreds of mRNAs or other ncRNAs are generally enriched as direct or indirect targets, and the coordination of many of these can be regulated to produce a series of biological consequences. Using this functional feature to our advantage, we took a data-driven approach and collected all the articles on CRC-related ncRNAs and miRNAs from PubMed in the last 5 years, and set IF > as the threshold. Next, we combined text mining and network statistical analysis, and set all ncRNAs and their target genes that appeared more than twice in the collected literature as nodes, and finally obtained a ncRNA regulatory network as presented this review (All steps of our approach are represented in **Figure 2** and the ncRNA regulatory network thus obtained is shown in **Figure 3**). Next, based on the number of ncRNA targets and the citations of related ncRNAs, we speculated its potential importance in the gene regulatory network for cancer, determined the final priority. Thereafter, we examined the interaction between the star ncRNAs targets, and the potential biological functions of ncRNAs in CRC. Detailed information on the network composition is shown in **Table 1**. The filtered nodes, which represent the un-replicated findings, are shown in **Table 2**. Through this review, we aimed to investigate the role of ncRNA regulatory network in the initiation and progression of CRC. Our review may have implications in future research strategies using ncRNAs in the treatment of CRC and tackling multi-drug resistance.

Classification of ncRNA Networks in Colorectal Cancer

Through the ncRNA network of colorectal cancer, we can clearly observe that the entire network graph is mainly divided into three large sub-networks (Including the miR-34a/b/c/miR-194-5p/miR21 sub-network, the CRNDE/EZH2/miR214/UCA1 sub-network and the miR-149/150-5p/LINC00460/miR-19a/20a sub-network) and a series of small networks (Including small networks with LNC00152, YAP, miR-27a, miR-24, miR-31, miR-7

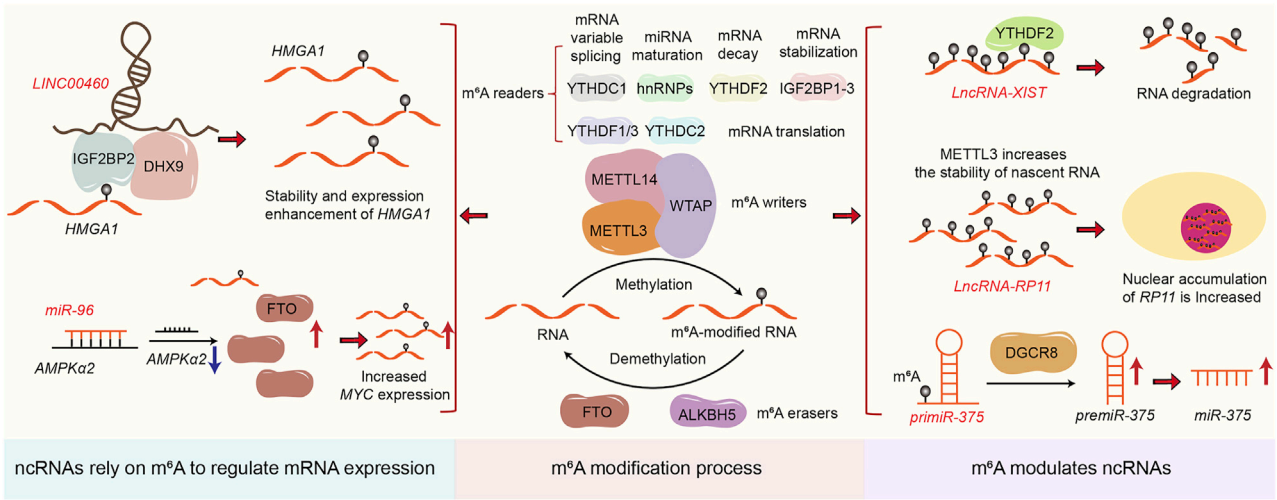

FIGURE 1 | The correlation between ncRNAs and m^{6}A modification. The figure shows how m^{6}A regulates ncRNAs expression and how ncRNAs rely on m^{6}A to regulate mRNA expression.

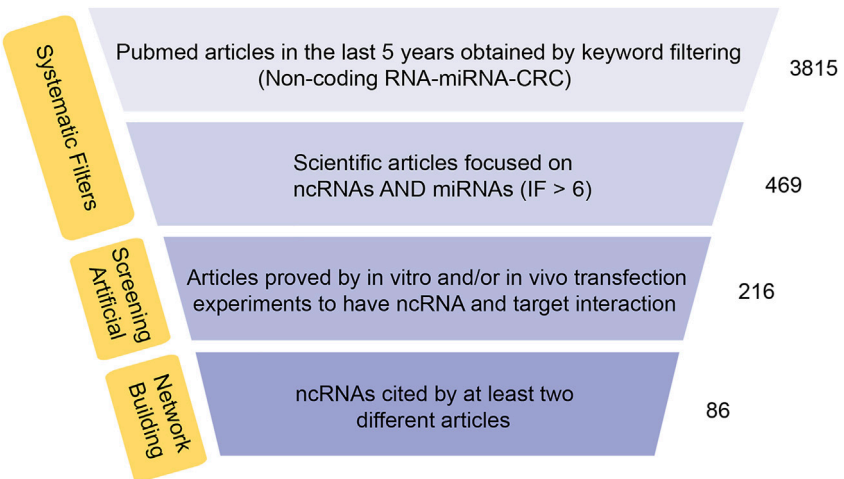

FIGURE 2 | Synthesis of data-approach used to build the network ncRNAs-target. Flow chart of RNA network construction.

as the core genes). Among these sub-networks, the miR-34a/b/c/miR-194-5p/miR21 sub-network and the LINC00152 network are mainly related to colorectal cancer chemotherapy resistance, which we call colorectal cancer chemotherapy resistance network; the CRNDE/EZH2/miR214/UCA1 sub-network, the YAP network and miR-24 network are mainly related to the metastasis of colorectal cancer, which we call the colorectal cancer metastasis network. These networks act synergistically and promote the progression of CRC (**Figure 4**; **Table 3**).

Chemotherapy Resistance Network of Colorectal Cancer

Chemotherapy resistance is one of the predominant reasons for the recurrence as well as poor prognosis of colorectal cancer (CRC) patients; ncRNAs reduce chemotherapy resistance of tumors by regulating signaling pathways in the initiation and progression of CRC. We integrated a variety of ncRNAs in CRC chemotherapy resistance and speculated that the combination of ncRNA-targeted inhibitors and chemotherapeutic drugs could be potential agents for improving the therapeutic effect of CRC.

The miR-34a/b/c/miR-194-5p/miR21 sub-network is the core chemotherapeutic resistance network in CRC treatment. The miR-34 family played a critical role in this sub-network by connecting multiple target proteins and lncRNAs. Furthermore, a number of reports show a reduced p53-induced miR-34 expression in CRC cells, and miR-34 can inhibit the occurrence and development of intestinal tumors. Moreover, miR-34 loss is related to tumor progression and chemotherapeutic resistance (Siemens et al., 2013). The mRNA

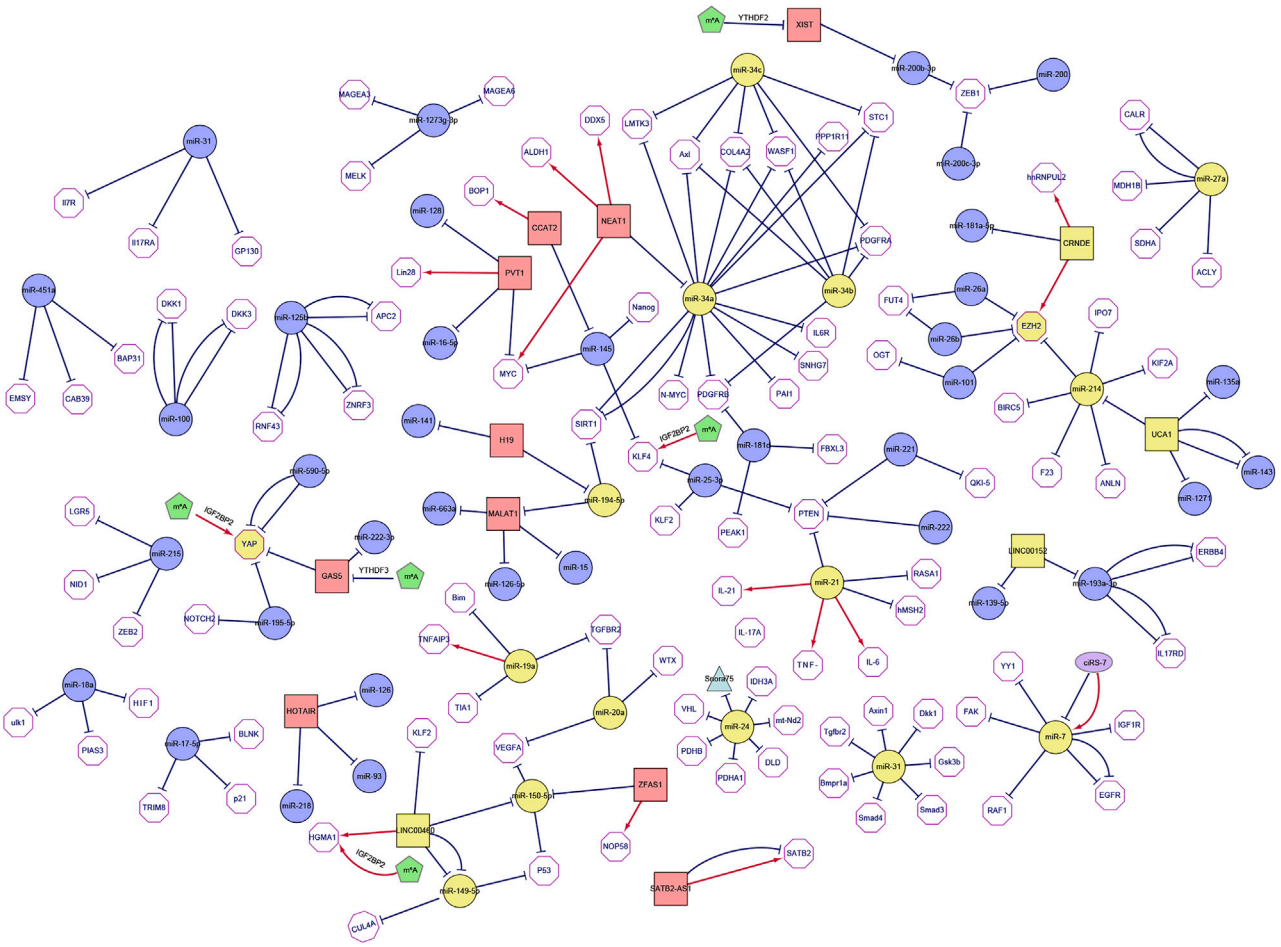

FIGURE 3 | The network of non-coding RNAs and its targets in colorectal cancer. The figure shows ncRNAs reported in at least two different literature sources (the squares represent long non-coding RNAs, the purple ellipses represent circular RNAs, the circles represent microRNAs, the triangles represent snoRNAs, the pentagon represents m^{6}A modification and yellow indicates core genes). The target mRNA of ncRNA is represented by a hexagon, and each target is reported in PUBMED. When the interaction is described in multiple articles, multiple line segments are drawn between the two nodes. The edges are directed (i.e., from the non-coding RNA to its target which could either be coding or non-coding). In the figure, red regular arrows indicate active links, and black flat arrows indicate inhibited links.

induction in miR-34a/b/c-deficient tumors was enriched in miR-34a/b/c seed-matching sites and mRNAs encoding proteins for Wnt signaling in epithelial-mesenchymal transition (EMT) and stemness such as INHBB, AXL, FGFR1 and PDFGRB, etc. This leads to a decrease in immune cell infiltration and down-regulation of barrier proteins, which in turn promote proliferation and inhibit apoptosis (Jiang and Hermeking, 2017). Meanwhile, studies show that miR-34 mimics can be utilized to stimulate target multiple key pathways, thereby preventing the emergence of drug resistance caused by mutations in a single pathway. The deletion of miR-34a also enhances the effects of TP53 deletion in the early or late stages during CRC initiation and progression. Additionally, miR-34a and TP53 can synergistically inhibit tumor initiation, invasion and metastasis in mouse models of CRC by increasing the levels of target proteins IL6R and PAI1 (Öner et al., 2018). PPP1R11 is also a target of miR-34a, and its product inhibits PP1. In p53-deficient CRC cells, PPP1R11 can activate the phosphorylation of STAT3, and simultaneously, high expression of PPP1R11 can induce EMT, invasion, migration and resistance to 5-fluorouracil under hypoxic conditions. Moreover, miR-34a can reduce the activation of STAT3 in p53-deficient CRC cells by decreasing the expression of PPP1R11, and ultimately inhibit EMT and metastasis of CRC cells (Li et al., 2017a). Thus, we speculate that inhibiting the expression of TP53 and miR-34a in CRC or using miR-34a/b/c replacement therapy may be a potential approach for CRC treatment. The antibodies or small molecule inhibitors to repress miR-34a targeting IL6R and PAI1 are potent promising treatment of CRC in the future.

Additionally, in this sub-network, we can find that KLF4 is significant related to miR-25-3p, and miR-25-3p, as an inhibitor of KLF4, has the effect of promoting the metastasis of CRC (Zeng et al., 2018a). A recent study further showed that MeCP2 bound to METTL14 and enhanced the m^{6}A level of KLF4, while m^{6}A-modified KLF4 was supposed to be stabilized by IGF2BP2 to increase the expression of KLF4, thereby

TABLE 1 | List of ncRNA-target and the type of interaction present in the network.

ncRNA	Direct target	Type of interaction	PMID	References
CCAT2	miR-145	neg	28964256	Yu et al. (2017a)
CCAT2	BOP1	pos	32805281	Chen et al. (2020c)
ciRS-7	miR-7	pos	32917870	Kristensen et al. (2020)
ciRS-7	miR-7	sponge	28174233	Weng et al. (2017)
CRNDE	EZH2	Pos	28796262	Ding et al. (2017a)
CRNDE	miR-181a-5p	Neg	28086904	Han et al. (2017)
CRNDE	hnRNPUL2	Shuttling neg	28594403	Jiang et al. (2017)
GAS5	YAP		31619268	Ni et al. (2019)
GAS5	miR-222−3p	Sponge	31400607	Liu et al. (2019a)
H19	miR-141	Sponge	30083271	Ren et al. (2018a)
H19	miR-194−5p	Sponge	30451820	Wang et al. (2018a)
HOTAIR	miR-218	Neg	28918035	Li et al. (2017b)
HOTAIR	miR-93	Sponge	32144238	Liu et al. (2020a)
HOTAIR	miR-126	Sponge	31974341	Jiang et al. (2020)
LINC00152	miR-193a-3p	Sponge	27633443	Yue et al. (2016)
LINC00152	miR-139−5p	Sponge	29180678	Bian et al. (2017)
LINC00460	miR-149−5p	Sponge	30092404	Lian et al. (2018)
LINC00460	miR-149−5p	Sponge	33251049	Meng et al. (2020)
LINC00460	miR-150−5p	Sponge	33251049	Meng et al. (2020)
LINC00460	KLF2	Neg	30092404	Lian et al. (2018)
MALAT1	miR-15	Sponge	31097689	Ji et al. (2019)
MALAT1	miR-126−5p	Sponge	30531836	Sun et al. (2019a)
MALAT1	miR-663a	Neg	30154407	Tian et al. (2018)
miR-100	DKK1	Neg	29035371	Lu et al. (2017)
miR-100	DKK3	Neg	29035371	Lu et al. (2017)
miR-100	DKK1	Neg	29094721	Thomas, (2017)
miR-100	DKK3	Neg	29094721	Thomas, (2017)
miR-101	OGT	Neg	30093632	Jiang et al. (2019)
miR-101	EZH2	Neg	30093632	Jiang et al. (2019)
miR-125b	ZNRF3	Neg	29035371	Lu et al. (2017)
miR-125b	RNF43	Neg	29035371	Lu et al. (2017)
miR-125b	APC2	Neg	29035371	Lu et al. (2017)
miR-125b	RNF43	neg	29094721	Thomas, (2017)
miR-125b	APC2	neg	29094721	Thomas, (2017)
miR-1273g-3p	MELK	neg	31358735	Zhao et al. (2019)
miR-1273g-3p	MAGEA3/6	neg	30056111	Wu et al. (2018)
miR-145	MYC	neg	29475734	Zhu et al. (2018a)
miR-145	KLF4	neg	29475734	Zhu et al. (2018a)
miR-145	Nanog	neg	29475734	Zhu et al. (2018a)
miR-149−5p	CUL4A	neg	30092404	Lian et al. (2018)
miR-149−5p	P53	neg	33251049	Meng et al. (2020)
miR-150−5p	P53	neg	33251049	Meng et al. (2020)
miR-150−5p	VEGFA	neg	30250022	Chen et al. (2018)
miR-17−5p	TRIM8	neg	28327152	Mastropasqua et al. (2017)
miR-17−5p	p21	neg	28327152	Mastropasqua et al. (2017)
miR-17−5p	BLNK	neg	30555542	Mai et al. (2018)
miR-181d	PDGFRB	neg	28363996	Jiang and Hermeking, (2017)
miR-181d	FBXL3	neg	28749470	Guo et al. (2017)
miR-181d	PEAK1	neg	29449544	Huang et al. (2018b)
miR-18a	ulk1	neg	28753429	Yu et al. (2017b)
miR-18a	PIAS3	neg	29896300	Ma et al. (2018)
miR-18a	HIF1α	neg	27080303	Ma et al. (2016a)
miR-193a-3p	IL17RD	neg	28600480	Pekow et al. (2017)
miR-193a-3p	ERBB4	neg	27633443	Yue et al. (2016)
miR-193a-3p	IL17RD	neg	28600480	Pekow et al. (2017)
miR-193a-3p	ERBB4	neg	27633443	Yue et al. (2016)
miR-194−5p	MALAT1	neg	31311811	Wu et al. (2019b)
miR-194−5p	SIRT1	neg	30451820	Wang et al. (2018a)
miR-195−5p	YAP	neg	28356122	Sun et al. (2017)
miR-195−5p	NOTCH2	neg	30808369	Lin et al. (2019a)
miR-19a	TGFBR2	neg	27080303	Ma et al. (2016a)
miR-19a	TIA1	neg	28257633	Liu et al. (2017a)
miR-19a	Bim	neg	32591507	Guo et al. (2020a)
miR-19a	TNFAIP3	pos	27991929	Wang et al. (2017a)

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TABLE 1 | (*Continued*) List of ncRNA-target and the type of interaction present in the network.

ncRNA	Direct target	Type of interaction	PMID	References
miR-200	ZEB1	neg	26455323	Barbáchano et al. (2016)
miR-200b-3p	ZEB1	neg	28837144	Chen et al. (2017a)
miR-200c-3p	ZEB1	neg	28535802	Rigoutsos et al. (2017)
miR-20a	TGFBR2	neg	27080303	Ma et al. (2016a)
miR-20a	VEGFA	neg	27080303	Ma et al. (2016a)
miR-20a	WTX	neg	30631060	Zhu et al. (2019)
miR-21	RASA1	neg	27876571	Yang et al. (2017)
miR-21	IL-6	pos	25994220	Shi et al. (2016)
miR-21	TNF-α	pos	25994220	Shi et al. (2016)
miR-21	IL-17A	pos	25994220	Shi et al. (2016)
miR-21	IL-21	pos	25994220	Shi et al. (2016)
miR-21	PTEN	neg	31918721	Liang et al. (2020a)
miR-21	hMSH2	neg	31918721	Liang et al. (2020a)
miR-214	EZH2	neg	30626446	Xu et al. (2019a)
miR-214	ANLN	neg	30195762	Barbagallo et al. (2018)
miR-214	F23	neg	30195762	Barbagallo et al. (2018)
miR-214	KIF2A	neg	30195762	Barbagallo et al. (2018)
miR-214	IPO7	neg	30195762	Barbagallo et al. (2018)
miR-214	BIRC5	neg	30195762	Barbagallo et al. (2018)
miR-215	NID1	neg	30831320	Rokavec et al. (2019)
miR-215	ZEB2	neg	29187907	Chen et al. (2017b)
miR-215	LGR5	neg	30790680	Ullmann et al. (2019)
miR-221	PTEN	neg	28986522	Antoniali et al. (2017)
miR-221	QKI-5	neg	31416845	Mukohyama et al. (2019)
miR-222	PTEN	neg	28986522	Antoniali et al. (2017)
miR-24	Snora75	neg	28500171	Michael et al. (2017)
miR-24	mt-Nd2	neg	28500171	Michael et al. (2017)
miR-24	VHL	neg	30393198	Jin et al. (2019)
miR-24	PDHB	neg	30393198	Jin et al. (2019)
miR-24	PDHA1	neg	30393198	Jin et al. (2019)
miR-24	DLD	neg	30393198	Jin et al. (2019)
miR-24	IDH3A	neg	30393198	Jin et al. (2019)
miR-25−3p	KLF2	neg	30568162	Zeng et al. (2018a)
miR-25−3p	KLF4	neg	30568162	Zeng et al. (2018a)
miR-25−3p	PTEN	neg	31931030	Wang et al. (2020a)
miR-26a	FUT4	neg	28640257	Li et al. (2017c)
miR-26a	EZH2	neg	30626446	Xu et al. (2019a)
miR-26b	FUT4	neg	28640257	Li et al. (2017c)
miR-26b	EZH2	neg	30626446	Xu et al. (2019a)
miR-27a	ACLY	neg	30393198	Jin et al. (2019)
miR-27a	MDH1B	neg	30393198	Jin et al. (2019)
miR-27a	SDHA	neg	30393198	Jin et al. (2019)
miR-27a	calreticulin	neg	26913599	Colangelo et al. (2016a)
miR-27a	calreticulin	neg	26913609	Colangelo et al. (2016b)
miR-31	Axin1	neg	28870287	Tian et al. (2017)
miR-31	Gsk3b	neg	28870287	Tian et al. (2017)
miR-31	Tgfbr2	neg	28870287	Tian et al. (2017)
miR-31	Bmpr1a	neg	28870287	Tian et al. (2017)
miR-31	Smad4	neg	28870287	Tian et al. (2017)
miR-31	Smad3	neg	28870287	Tian et al. (2017)
miR-31	Dkk1	neg	28870287	Tian et al. (2017)
miR-31	Il7R	neg	30779922	Tian et al. (2019)
miR-31	Il17RA	neg	30779922	Tian et al. (2019)
miR-31	GP130	neg	30779922	Tian et al. (2019)
miR-34a	IL6R	neg	30099074	Öner et al. (2018)
miR-34a	PAI1	neg	30099074	Öner et al. (2018)
miR-34a	PPP1R11	neg	28435028	Li et al. (2017a)
miR-34a	SNHG7	neg	29970122	Li et al. (2018a)
miR-34a	N-MYC	neg	28327152	Mastropasqua et al. (2017)
miR-34a	Pdgfra	neg	28363996	Jiang and Hermeking, (2017)
miR-34a	Axl	neg	28363996	Jiang and Hermeking, (2017)
miR-34a	COL4A2	neg	28363996	Jiang and Hermeking, (2017)
miR-34a	WASF1	neg	28363996	Jiang and Hermeking, (2017)
miR-34a	STC1	neg	28363996	Jiang and Hermeking, (2017)

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TABLE 1 | (*Continued*) List of ncRNA-target and the type of interaction present in the network.

ncRNA	Direct target	Type of interaction	PMID	References
miR-34a	PDGFRB	neg	28363996	Jiang and Hermeking, (2017)
miR-34a	SIRT1	neg	30312725	Luo et al. (2019)
miR-34a	SIRT1	neg	28943452	Fang et al. (2017)
miR-34a	LMTK3	neg	26739063	Jacob et al. (2016)
miR-34b	Pdgfra	neg	28363996	Jiang and Hermeking, (2017)
miR-34b	Axl	neg	28363996	Jiang and Hermeking, (2017)
miR-34b	COL4A2	neg	28363996	Jiang and Hermeking, (2017)
miR-34b	WASF1	neg	28363996	Jiang and Hermeking, (2017)
miR-34b	STC1	neg	28363996	Jiang and Hermeking, (2017)
miR-34b	PDGFRB	neg	28363996	Jiang and Hermeking, (2017)
miR-34c	LMTK3	neg	26739063	Jacob et al. (2016)
miR-34c	Pdgfra	neg	28363996	Jiang and Hermeking, (2017)
miR-34c	Axl	neg	28363996	Jiang and Hermeking, (2017)
miR-34c	COL4A2	neg	28363996	Jiang and Hermeking, (2017)
miR-34c	WASF1	neg	28363996	Jiang and Hermeking, (2017)
miR-34c	STC1	neg	28363996	Jiang and Hermeking, (2017)
miR-451a	EMSY	neg	28742699	Kelley et al. (2017)
miR-451a	CAB39	neg	28742699	Kelley et al. (2017)
miR-451a	BAP31	neg	30770794	Xu et al. (2019b)
miR-590−5p	YAP	neg	29912317	Yu et al. (2018a)
miR-590−5p	YAP	neg	29429755	Ou et al. (2018)
miR-7	EGFR	neg	28174233	Weng et al. (2017)
miR-7	RAF1	neg	28174233	Weng et al. (2017)
miR-7	FAK	neg	29549306	Zeng et al. (2018b)
miR-7	IGF1R	neg	29549306	Zeng et al. (2018b)
miR-7	EGFR	neg	29549306	Zeng et al. (2018b)
miR-7	YY1	neg	29549306	Zeng et al. (2018b)
NEAT1	ALDH1	pos	33168814	Zhu et al. (2020a)
NEAT1	MYC	pos	33168814	Zhu et al. (2020a)
NEAT1	miR-34a	sponge	30312725	Luo et al. (2019)
NEAT1	DDX5	pos	30185232	Zhang et al. (2018a)
PVT1	MYC	neg	33148262	Shigeyasu et al. (2020)
PVT1	miR-16−5p	neg	32276209	Wu et al. (2020a)
PVT1	Lin28	pos	30076414	He et al. (2019)
PVT1	miR-128	sponge	30076414	He et al. (2019)
SATB2-AS1	SATB2	neg	30858153	Wang et al. (2019a)
SATB2-AS1	SATB2	pos	31492160	Xu et al. (2019c)
UCA1	miR-143	sponge	31955010	Luan et al. (2020)
UCA1	miR-135a	sponge	30195762	Barbagallo et al. (2018)
UCA1	miR-143	sponge	30195762	Barbagallo et al. (2018)
UCA1	miR-214	sponge	30195762	Barbagallo et al. (2018)
UCA1	miR-1271	sponge	30195762	Barbagallo et al. (2018)
ZFAS1	NOP58	pos	32443980	Wu et al. (2020b)
ZFAS1	miR-150−5p	sponge	30250022	Chen et al. (2018)

inhibiting the metastasis of CRC (Wang et al., 2021). Therefore, the development of drugs that simultaneously target to promote the expression of IGF2BP2 and target to inhibit the expression of miR-25-3p may be also an important approach for the treatment of CRC.

SNHG7 (small nucleolar RNA host gene 7), miR-34a and GALNT7 also play an important role in the progression of CRC through the PI3K/AKT/mTOR pathway. SNHG7 can be used as a competitive endogenous RNA (ceRNAs). Along with the sponge miR-34a, it can regulate the level of GALNT7 in CRC and activate the PI3K/AKT/mTOR pathway to promote proliferation and metastasis (Li et al., 2018a). Mastropasqua et al. report that TRIM8 (tripartite motif containing 8) and its regulatory factors including miR-17-5p and miR-106b-5 participate in a feedback loop that controls cell proliferation in CRC by mutual regulation of p53, miR-34a, and N-Myc. In CRC, TRIM8 is a key target that triggers the sensitivity of CRC cells to chemotherapy. TRIM8 restores the function of the p53 tumor suppressor by inactivating the activity of oncoprotein N-Myc in chemotherapy-resistant tumors. Additionally, the silencing of miR-17-5p and miR-106b-5p restore the levels of TRIM8, and effectively promote the tumor suppressor activity of p53 and the transcription of miR-34a, thereby reducing the carcinogenic potential of miR-34a's target N-Myc. It restores the sensitivity of cells to chemotherapy (Mastropasqua et al., 2017). In addition, LMTK3 (lemur tyrosine kinase 3), an important node in the network diagram, plays an important role in the progression of a variety of cancers (breast cancer, lung cancer, CRC, etc.) (Xu et al., 2014; Xu et al., 2015). In CRC, nuclear LMTK3 interacts with DDX5 to target and regulate the expression of a group of

TABLE 2 | List of ncRNAs, their targets and the type of interactions, cited by only one scientific article.

ncRNA	Target	Type of interaction	PMID	References
ADAMTS9-AS2	miR-143−3p	sponge	30217729	Xie et al. (2018)
AK000053	miR-508	sponge	29374066	Yan et al. (2018)
AK036396	Ficolin B	neg	32102837	Tian et al. (2020)
ASBEL	ATF3	neg	27791078	Taniue et al. (2016a)
BC032913	TIMP3	pos	28918047	Lin et al. (2017)
BFAL1	miR-155−5p, miR-200a-3p	sponge	31515468	Bao et al. (2019)
BLACAT1	EZH2, p15	Cooperate, neg	28277544	Su et al. (2017)
CALIC	hnRNP-L, AXL	Cooperate, pos	31353791	Kawasaki et al. (2019)
CASC11	hnRNP-K	pos	27012187	Zhang et al. (2016a)
CCAL	AP-2α	neg	25994219	Ma et al. (2016b)
circ101555	miR-597−5p	sponge	31300733	Chen et al. (2019b)
circ5615	miR-149−5p	sponge	32393760	Ma et al. (2020)
circACC1	AMPK	pos	31155494	Li et al. (2019)
circCTNNA1	miR-149−5p	sponge	32699205	Chen et al. (2020b)
circHIPK3	miR-7	neg	29549306	Zeng et al. (2018b)
CYTOR	β-catenin	pos	29606502	Yue et al. (2018)
FARSA-AS1	miR-18b-5p	sponge	33318478	Zhou et al. (2020)
FEZF1-AS1	PKM2	pos	29914894	Bian et al. (2018)
FLANC	pSTAT3	pos	31988194	Pichler et al. (2020)
FOXC2-AS1	FOXC2	pos	32513911	Pan and Xie, (2020)
GLCC1	c-Myc	pos	31375671	Tang et al. (2019a)
GSEC	DHX36	neg	27797375	Matsumura et al. (2017)
HITT	HIF-1α	neg	31784651	Wang et al. (2020b)
HNF1A-AS1	miRNA-34a	sponge	28943452	Fang et al. (2017)
HOXA-AS2	p21, KLF2, EZH2	neg, neg, cooperate	28112720	Ding et al. (2017b)
HOXD-AS1	HOXD3	neg	30823921	Yang et al. (2019)
ITHI4-AS1	JAK1/2, FUS	pos	31557619	Liang et al. (2019a)
KRT7-AS	KRT7	pos	31910722	Chen et al. (2020d)
LDLRAD4-AS1	LDLRAD4	neg	32111819	Mo et al. (2020)
LINC00265	ZMIZ2	pos	31527801	Zhu et al. (2020b)
LINC00659	PI3K	pos	29523145	Tsai et al. (2018)
LINC00858	miR-4766−5p	sponge	31902050	Zhan et al. (2020)
LINC01106	miR-449b-5p	sponge	33067422	Guo et al. (2020b)
LINC01133	SRSF6	sponge	27443606	Kong et al. (2016)
LINC01234	miR-642a-5p	sponge	30755591	Lin et al. (2019b)
LINC01413	hnRNPK, ZEB1	cooperate, pos	31927328	Ji et al. (2020)
LINC01578	NFKBIB	neg	33040438	Liu et al. (2020b)
LINC02023	PTEN	pos	30849479	Wang et al. (2019b)
LINC02418	miR-1273g-3p	sponge	31358735	Zhao et al. (2019)
LINC-UFC1	β-catenin	pos	27195675	Yu et al. (2016)
LINRIS	IGF2BP2	pos	31791342	Wang et al. (2019c)
LNC34a	miR-34a	neg	27077950	Wang et al. (2016a)
LNC-C/EBPβ	Arg1, CYBB, NOS2, ptgs2	neg	30171135	Gao et al. (2018)
LNC-CMPK2	FUBP3	pos	32203166	Gao et al. (2020)
LNC-CRCMSL	HMGB2	shuttling	30575817	Han et al. (2019)
LNC-FAM84B-4	hnRNPK, DUSP1	cooperate, neg	32866608	Peng et al. (2020)
LNC-Gata6	Lgr4, Lgr5	pos	30224759	Zhu et al. (2018b)
LNC-RI	miR-4727−5p	sponge	32279126	Liu et al. (2020c)
LncRNA-APC1	Rab5b	pos	30511962	Wang et al. (2019d)
LNRRIL6	IL-6	pos	31246342	Wang et al. (2019e)
LUCAT1	NCL	binding	33097685	Wu et al. (2020c)
miR-342	FOXM1, FOXQ1	neg	27162244	Weng et al. (2016)
miR-101c	Tet1	neg	28249902	Tie et al. (2017)
miR-105	RAP2C	neg	29238068	Shen et al. (2017a)
miR-106a	WTX	neg	30631060	Zhu et al. (2019)
miR-106b-5p	TRIM8, p21	neg	28327152	Mastropasqua et al. (2017)
miR-10a	ACTG1, MMP14	neg	28383561	Liu et al. (2017b)
miR-124	iASPP	neg	29022915	Liu et al. (2017c)
miR-1249	HMGA2, VEGFA	neg	30755600	Chen et al. (2019c)
miR-125a-3p	FUT5, FUT6	neg	28771224	Liang et al. (2017)
miR-126	SCEL	neg	31974341	Jiang et al. (2020)
miR-126−5p	VEGFA, TWIST, SLUG	neg	30531836	Sun et al. (2019a)
miR-1271	ANLN, BIRC5, IPO7, KIF2A, F23	neg	30195762	Barbagallo et al. (2018)
miR-128	Lin28	neg	30076414	He et al. (2019)
miR-128−3p	Bmi1, MRP5	neg	30890168	Liu et al. (2019b)

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TABLE 2 | (*Continued*) List of ncRNAs, their targets and the type of interactions, cited by only one scientific article.

ncRNA	Target	Type of interaction	PMID	References
miR-130b-3p	PTEN	neg	31931030	Wang et al. (2020a)
miR-135a	ANLN, BIRC5, IPO7, KIF2A, F23	neg	30195762	Barbagallo et al. (2018)
miR-137	GLS1	neg	29730197	Li et al. (2018b)
miR137HG	mir-137	pos	29730197	Li et al. (2018b)
miR-139−5p	PDE4D	neg	27383270	Cao et al. (2016)
miR-141	β-catenin	neg	30083271	Ren et al. (2018a)
miR-141−3p	ZEB1	neg	28535802	Rigoutsos et al. (2017)
miR-143	ANLN, BIRC5, IPO7, KIF2A, F23	neg	30195762	Barbagallo et al. (2018)
miR-143−3p	ITGA6	neg	30217729	Xie et al. (2018)
miR-144	EZH2	neg	30770796	Shi et al. (2019)
miR-146a	c-met	neg	29133238	Bleau et al. (2018)
miR-148a	GP130, IL1R1, IKKα, IKKβ, TNFR2	neg	28960206	Zhu et al. (2017)
miR-149	CDK4/6, XIAP, BCLXL, cyclin D	neg	29061672	Lulla et al. (2017)
miR-149−3p	PDK2	neg	31597953	Liang et al. (2020b)
miR-15	LRP6	neg	31097689	Ji et al. (2019)
miR-150	ZEB1	neg	26455323	Barbáchano et al. (2016)
miR-153	IDO1	neg	29685162	Huang et al. (2018c)
miR-15b	DCLK1	Neg	30449704	Ji et al. (2018)
miR-16−5p	VEGFR1	Pos	32276209	Wu et al. (2020a)
miR17HG	miR-375	Sponge	31409641	Xu et al. (2019d)
miR-181a	SRCIN1	Neg	29739921	Sun et al. (2018)
miR-181a-5p	β-catenin, TCF4	Neg	28086904	Han et al. (2017)
miR-181b	PDCD4	Neg	27647131	Liu et al. (2016)
miR-182	LMTK3	Neg	26739063	Jacob et al. (2016)
miR-187	SOX4, PTK6, NT5E	Neg	26820227	Zhang et al. (2016b)
miR-18b-5p	FARSA	Neg	33318478	Zhou et al. (2020)
miR-193a	Caprin1	Neg	28211508	Teng et al. (2017)
miR-194	VAPA	Neg	29109785	Chang et al. (2017)
miR-195	WEE1, CHK1	Neg	29080751	Kim et al. (2018)
miR-196b-5p	HOXB7, GALNT5	Pos	28533224	Stiegelbauer et al. (2017)
miR-19b	Bim	Neg	32591507	Guo et al. (2020a)
miR-200a-3p	RHEB	Neg	31515468	Bao et al. (2019)
miR-203	BIRC5	Neg	31091026	Okugawa et al. (2019)
miR-205−5p	ZEB1	Neg	29352232	Gulei et al. (2018)
miR-206	Met	Neg	30250188	Xu et al. (2018a)
miR-214−3p	MyD88	Neg	30914411	Shang et al. (2019)
miR-215−5p	EREG, TYMS	Neg	31542354	Chen et al. (2019d)
miR-216b	GALNT1	Neg	29915311	Shan et al. (2018)
miR-218	VOPP1	Neg	28918035	Li et al. (2017b)
miR-22	HuR	Neg	29351796	Liu et al. (2018a)
miR-222−3p	PTEN	Neg	31400607	Liu et al. (2019a)
miR-223	FBX8	Neg	27916606	Wang et al. (2017b)
miR-224	SMAD4	Neg	25804630	Ling et al. (2016)
miR-23a	CS, PDHA1, IDH1, DLD	Neg	30393198	Jin et al. (2019)
miR-23b	LGR5	Neg	28487386	Viswanathan et al. (2017)
miR-301A	BTG1	Neg	28193514	He et al. (2017)
miR-302a	NFIB, CD44	Neg	31754405	Sun et al. (2019b)
miR-30a	ME1	Neg	28475173	Shen et al. (2017b)
miR-30a-5p	LDHA	Neg	28461244	Li et al. (2017d)
miR-320a	PKCγ	Neg	31515469	Aljagthmi et al. (2019)
miR-338−5p	IL-6	Neg	31208913	Xu et al. (2019e)
miR-372/373	SPOP, VDR, SETD7, RELA TRERF1, ZNF367, MTUS1	Neg	30171794	Wang et al. (2018b)
miR-375	RELA, MALT1, NFKBIE PPP3R1, MAP3K7, CBL	Neg	31409641	Xu et al. (2019d)
miR-425−5p	PTEN	Neg	31931030	Wang et al. (2020a)
miR-4260	MCC, SMAD4	Neg	28638476	Xiao et al. (2017)
miR-448	IDO1	Neg	31391111	Lou et al. (2019)
miR-449b-5p	Gli4	Neg	25961913	Wang et al. (2016b)
miR-4727−5p	LIG4	Neg	32279126	Liu et al. (2020c)
miR-4766−5p	PAK2	Neg	31902050	Zhan et al. (2020)
miR-4775	Smad7	Neg	28095858	Zhao et al. (2017)
miR-4802	ATG7	Neg	28753429	Yu et al. (2017b)
miR-486−5p	PLAGL2	Neg	30305607	Liu et al. (2018b)

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TABLE 2 | (*Continued*) List of ncRNAs, their targets and the type of interactions, cited by only one scientific article.

ncRNA	Target	Type of interaction	PMID	References
miR-487b-3p	GRM3	Neg	28114282	Yi et al. (2017)
miR-490−3p	FRAT1	Neg	27037061	Zheng et al. (2016)
miR-494	APC	Neg	29304823	Zhang et al. (2018b)
miR-500a-5p	HDAC2	Neg	30737378	Tang et al. (2019b)
miR-508	SALL4	Neg	29374066	Yan et al. (2018)
miR-514b-3p	FZD4, NTN1	Neg	29880874	Ren et al. (2018b)
miR-514b-5p	CDH1, CLDN1	Neg	29880874	Ren et al. (2018b)
miR-532−3p	ETS1	Neg	31570702	Gu et al. (2019a)
miR-532−5p	TGFBR1	Neg	29971498	Gu et al. (2019b)
miR-550a-3-5p	YAP	Neg	29844307	Choe et al. (2018)
miR-550a-5p	RNF43	neg	25961913	Wang et al. (2016b)
miR-5582−5p	GAB1, CDK2, SHC1	neg	27475256	An et al. (2016)
miR574−5p	APAF1	neg	32784109	Wu et al. (2020d)
miR-597−5p	CDK6, RPA3	neg	31300733	Chen et al. (2019b)
miR-625−3p	MAP2K6	neg	27526785	Rasmussen et al. (2016)
miR-642a-5p	SHMT2	neg	30755591	Lin et al. (2019b)
miR-655−3p	TGFBR2, ICK	neg	28457664	Oshima et al. (2017)
miR-663a	TGFB1, PIK3CD, P53, JUND, P21	neg	30154407	Tian et al. (2018)
miR-675−5p	TP53	neg	31734182	Cen et al. (2020)
miR-6883−5p	CDK4/6, XIAP, BCLXL, cyclin D	neg	29061672	Lulla et al. (2017)
miR-92a-3p	FBXW7, MOAP1	neg	31064356	Hu et al. (2019)
miR-93	ATG12	neg	32144238	Liu et al. (2020a)
miR-944	COP1, MDM2	neg	30393117	Kim et al. (2019b)
MYU	miR-16	neg	27568568	Kawasaki et al. (2016)
N-BLR	miR-141−3p, miR-200c-3p	neg	28535802	Rigoutsos et al. (2017)
OLA1P2	STAT3	neg	26898989	Guo et al. (2016)
Olfr29-ps1	miR-214−3p	sponge	30914411	Shang et al. (2019)
OVAAL	PTBP1	neg	30478051	Sang et al. (2018)
PiHL	RPL11, GRWD1	pos	31903119	Deng et al. (2020)
PINCR	Matrin3	neg	28580901	Chaudhary et al. (2017)
piR-1245	ATF3, BTG1, DUSP1, NFKBIA,FAS, UPP1, SESN2, TP53INP1,MDX1	neg	29382334	Weng et al. (2018)
pirl -54265	p-STAT3, BCL-XL,cleaved-CASP3/7/9	Pos, pos, neg	30555542	Mai et al. (2018)
RAMS11	CBX4	pos	32358485	Silva-Fisher et al. (2020)
RBM5-AS1	CMYC, CCND1, YAP1, SGK1	pos	27520449	Di Cecilia et al. (2016)
RPPH1	TUBB3	pos	31685807	Liang et al. (2019b)
SNHG1	miR-154−5p	sponge	30266084	Xu et al. (2018b)
SNHG5	SPATS2	pos	28004750	Damas et al. (2016)
SNHG6	miR-26a, miR-26b, miR-214	sponge	30626446	Xu et al. (2019a)
SNHG7	miR-216b	sponge	29915311	Shan et al. (2018)
SNHG11	HIF-1α	sponge	33060856	Xu et al. (2020a)
SNHG14	miR-186−5p, EZH2	sponge, pos	31273190	Di et al. (2019)
SNHG15	Slug	pos	29604394	Jiang et al. (2018)
SNORA42	SMAD2	pos	32127004	Xu et al. (2020b)
SNORD12C/78	EIF4A3, LAMC2	pos	32443980	Wu et al. (2020b)
tcon_00012883	MMP1	pos	33135346	Yang et al. (2020b)
TUG1	TWIST1	pos	1988275	Mosthaf et al. (1991)
u50535	CCL20	pos	29970882	Yu et al. (2018b)
UICLM	miR-215	sponge	29187907	Chen et al. (2017b)
UPAT	UHRF1	pos	26768845	Taniue et al. (2016b)
WiNTRLINC1	ASCL2	pos	27292638	Giakountis et al. (2016)
ZNFX1-AS1	miR-144	sponge	30770796	Shi et al. (2019)
δNp63α	miR-320a	pos	31515469	Aljagthmi et al. (2019)

miRNAs (miR-34a, miR-196a2, and miR-182). The tumor suppressor-like miRNAs, miR-34a and miR-182 directly bind to the 3′UTR of LMTK3 mRNA and inhibit its stability and translation, thereby inhibiting the proliferation, invasion, and migration in CRC (Jacob et al., 2016).

In addition to targeting some encoded proteins, miR-34a could also target long-chain non-coding RNAs, and played an important regulatory role in the progression of CRC. NEAT1 (nuclear paraspeckle assembly transcript 1), a long-chain non-coding RNA, is a known oncogene in CRC. For example, NEAT1 can directly interact with its target DDX5 and stabilizes its protein expression. DDX5, thus, activates the Wnt/β-catenin signaling pathway and promotes the progression of CRC (Zhang et al., 2018a). Additionally, some studies show that NEAT1 is associated with 5-FU resistance in CRC. NEAT1 increases H3K27ac enrichment at ALDH1 and c-Myc promoters by

altering chromatin remodeling, thereby up-regulating their expression, enhancing the stemness of CRC cells, and promoting 5-FU resistance (Zhu et al., 2020a). Thus, NEAT1 plays an important role in tumor resistance and tumorigenesis in CRC.

However, the effect of NEAT1 on the Wnt/β-catenin signaling pathway is not completely dependent on DDX5, and NEAT1 can also exert carcinogenic effects through miR-34a (Luo et al., 2019). In CRC, NEAT1 acts as a ceRNA that targets miR-34a and regulates its expression, thereby inhibiting the miR-34a/SIRT1 axis. It activates the Wnt/β-catenin signaling pathway, and inhibits miR-34a/SIRT1 feedback loop, which in turn promotes CRC progression, invasion, and metastasis, etc. The above studies show that NEAT1 can be used as a diagnostic marker and is a potential therapeutic target for CRC. Moreover, traditional chemotherapy combined with drugs targeting tumor stem cells provides a new strategy for the treatment of CRC patients CRC patients with high NEAT1 expression. More importantly, the combined network analysis showed that miR-34 may simultaneously target different genes and multiple core pathways in CRC, inhibit EMT, invasion, migration, and proliferation of cancer cells, and prevent the emergence of drug resistance caused by mutations in a single pathway. Therefore, miR-34 replacement therapy could also be a potential option for the treatment of CRC. In addition, targeting a certain pathway regulated by miR-34 for specific effects could also be a potential direction for further research in the treatment of CRC.

In addition to NEAT1, the network diagram also connects a series of other long non-coding RNAs through different target genes. Indeed, there are several studies confirming the role of these long non-coding RNAs in CRC. Therefore, the interaction of different lncRNAs in CRC and their target proteins in this network require in-depth analysis. For example, some studies show that H19 may be the main marker for predicting 5-FU chemotherapy resistance. H19 acts as a ceRNA to target miR-194-5p, and in turn regulates the SIRT1-dependent autophagy pathway which promotes 5-FU chemotherapy resistance in CRC (Wang et al., 2018a). Autophagy is triggered by the target protein of miR-34a, SIRT1 in this network diagram too. Some studies show that H19 acts as a ceRNA sponge of miR-141, activates the β-catenin pathway and promotes stemness as well as chemotherapy resistance of CRC by transferring H19 from exosomes (Ren et al., 2018a). The above studies suggest that conventional chemotherapy combined with targeted therapy can be a potential treatment for 5-FU resistant patients with elevated expression of H19. From the network diagram, we observe that the sub-network highlights another branch of miR-194-5p, which can directly target the lncRNAs-MALAT1 harboring the rs664589 G allele in the nucleus of CRC cells, thereby regulating the nuclear expression of MALAT1 and exerting a tumor suppressor effect (Ren et al., 2018a). Researchers indicate that in CRC, the rs664589 polymorphism of MALAT1 inhibits its affinity to miR-194-5p, resulting in its increased expression, and thus, promotes the development of CRC. Moreover, MALAT1 is primarily induced by YAP1 in CRC and YAP1 interacts with TCF4 and β-catenin to regulate the expression of MALAT1 (Sun et al., 2019a). MALAT1 also primarily functions as a competitive endogenous lncRNA in CRC, which targets and regulates the sponging of miR-126-5p, miR-663a, miR-15, and other microRNAs to exhibit a tumor suppressor effect. MALAT1 promotes the expression of VEGFA, SLUG, TWIST, and other metastasis-related molecules by regulating the sponge miR-126-5p; it regulates the angiogenesis and EMT of CRC cells and promotes metastasis (Sun et al., 2019a). Additionally, MALAT1 protects the targets of miR-663a from degradation. MiR-663a and MALAT1 may form a negative feedback loop and affect the progression of CRC (Tian et al., 2018). MALAT1 functions as a ceRNA to regulate the miR-15 family. MiR-15 family inhibits the expression of LRP6 and the activation of the downstream β-catenin signaling pathway. MALAT1 regulates the transcription of the proto-oncogene RUNX2 through the miR-15s/LRP6/β-catenin signaling pathway and thus, regulates the progression of CRC (Ji et al., 2019).

Thereafter, we focus on the last lncRNA-PVT1 of the network diagram. PVT1, a previously unknown transcriptional regulator in CRC, shows a significantly high enhancer activity controlled by epigenetic regulation due to abnormal methylation involved in the occurrence and development of CRC. Enhanced expression of PVT1 is associated with the poor survival in CRC patients with clinical stage II or III status. It also exerts its function as a novel epigenetic enhancer of MYC and responsible for regulating the expression of oncogenic MYC gene (Shigeyasu et al., 2020). Furthermore, PVT1 also functions as a ceRNA to regulate the expression of target genes in the cytoplasm. For example, it can promote the proliferation and invasion of CRC cells by stabilizing Lin28 and interacting with miR-128 (He et al., 2019). Another study reported that PVT1 also promoted the specific binding of RNA-binding proteins (Lin28 and Lin28B) to let-7 by the up-regulation of Lin28 for driving carcinogenic activity of CRC; PVT1 stabilizes and post-transcriptionally regulates Lin28, which targets the Lin28/let-7 axis and promotes tumorigenesis. It is also speculated that the low expression of PVT1 in CRC inhibits EMT and angiogenesis. PVT1 promotes the occurrence of CRC by stabilizing miR-16-5p targeting the VEGFA/VEGFR1/AKT axis. Vascular endothelial growth factor A (VEGFA) is the direct downstream target of miR-16-5p. In the absence of PVT1-miR-16-5p/VEGFA/VEGFR1/AKT, signaling pathway is inactive, thereby inhibiting the progression of CRC (Wu et al., 2020a). In sum, targeting PVT1 may be a potential treatment option for CRC patients.

MiR-21 is also observed as an important multi-target miRNA in this network. Fusobacterium activates the toll-like receptor 4 signaling pathway, which leads to the activation of nuclear factor kappa B (NFκb) and up-regulation of miR-21 expression. Up-regulation of miR-21 reduces the level RAS GTPase (RASA1) and promotes the occurrence and development of CRC (Yang et al., 2017). In mice, silencing miR-21 results in a significant decrease in the expression of pro-inflammatory and cancer-promoting factors (IL6, IL-23, IL-17a and IL-21) and inhibition of tumor proliferation. Studies show that the absence of miR-21 leads to the decrease in Ki67 expression and the inhibition of tumor growth in colitis-associated colon cancer (CAC) mouse, an up-regulation of E-cadherin, and the downregulation of β-catenin and SOX9. The deletion of miR-21 increases the expression of its target gene PDCD4,

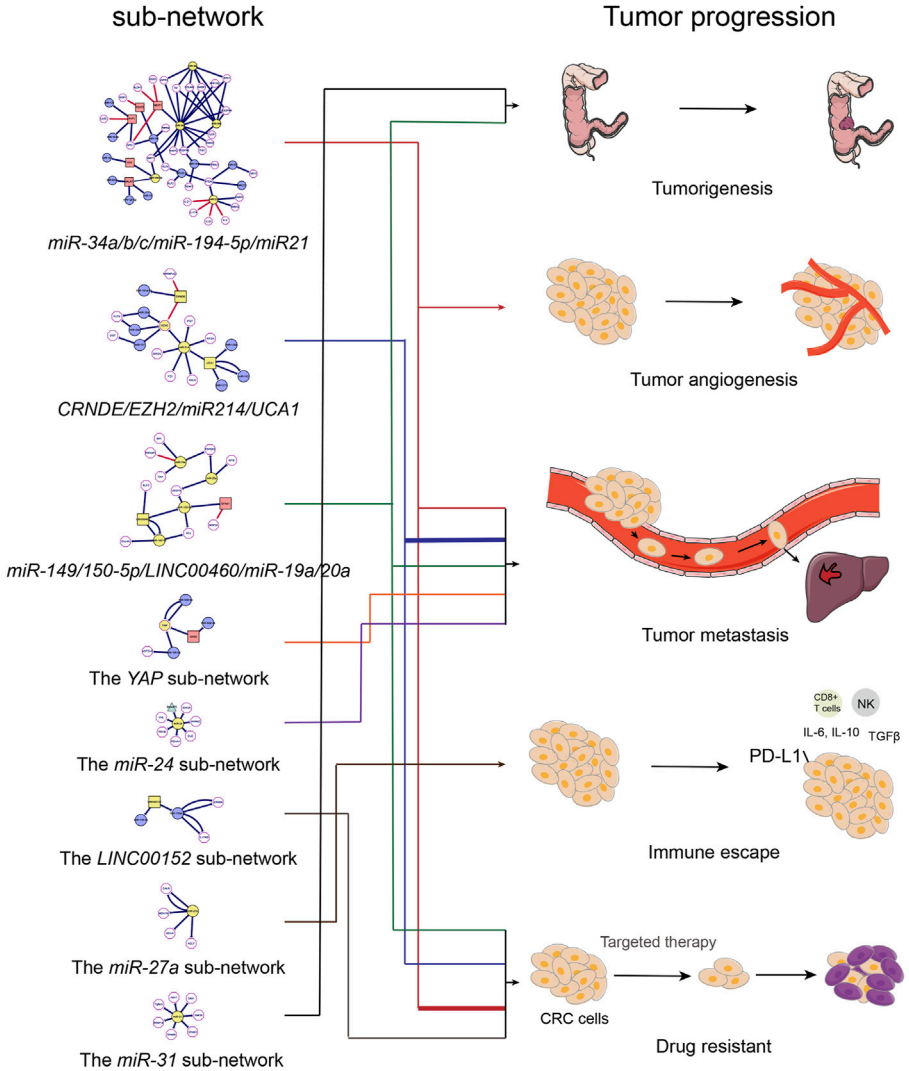

FIGURE 4 | The relationship between ncRNAs network and the progression of colorectal cancer. Diagram of the relationship between ncRNAs sub-network and colorectal cancer progression.

which in turn regulates the activation of NFκb. The deletion of miR-21 also inhibits the activation of STAT3 and Bcl-2 in CAC mice, leading to an increase in tumor cell apoptosis. These studies indicate the regulatory role of miR-21 in the development of CAC caused by colitis (Shi et al., 2016). Moreover, other studies show that miR-21 is correlated with chemotherapeutic resistance of CRC. MiR-21 regulates the expression of downstream targets PTEN and hMSH2, induces tumor cell cycle arrest, inhibits tumor cell proliferation, promotes cell apoptosis, and inhibits migration. MiR-21 targeted therapy can significantly enhance the cytotoxicity of 5-FU in resistant CRC cells and reverse the resistance in CRC just like the exosomal delivery of 5-FU (Liang et al., 2020a).

In the entire chemotherapy resistance network, LINC00152 acting as a ceRNA targets and regulates the expression of miR-193a-3p, antagonizes chemotherapy sensitivity, regulates erb-b2 receptor tyrosine kinase 4 (ERBB4), reduces the phosphorylation of AKT, and thereby reduces resistance to L-OHP (Yue et al., 2016). Similarly, it regulates the expression of NOTCH1 by inhibiting the activity of miR-139-5p, and increasing the resistance of CRC cells to 5-FU (Bian et al., 2017). These studies suggest that the Linc00152/miR-193a-3p/ERBB4/AKT and the LINC00152/miR-139-5p/NOTCH1 signaling axes may provide new insights into CRC resistance mechanisms. In addition, LINC00152 may also be a key tumor suppressor of ulcerative colitis-related CAC. Studies show that miR-193a-3p regulates the expression of IL17RD and controls the downstream EGFR signaling and inhibits the growth of colon cancer (Pekow et al., 2017). Thus, LINC00152 might be a novel potential target in the inflammation-driven CRC patients.

Metastasis Sub-network of Colorectal Cancer

The metastasis of CRC is the main reason for the poor clinical outcomes and high mortality for CRC patients. The CRNDE/

TABLE 3 | The relationship between ncRNAs network and the progression of colorectal cancer.

ncRNA network		Tumorigenesis	Tumor angiogenesis	Tumor metastasis	Immune escape	Drug resistant
The miR-34a/b/c/miR-194−5p/miR-21 sub-network	miR-34					PMID 24009080
	miR-194−5p					PMID 30451820
	miR-21					PMID 31918721
The CRNDE/EZH2/UCA1 sub-network	CRNDE					PMID 28086904
	EZH2			PMID 27638307		
	UCA1			PMID 31955010		
The miR-149/150−5p/LINC00460/miR-19a/20a sub-network	miR-149−5p		PMID 30531836			PMID 33251049
	miR-150−5p					PMID 33251049
	LINC00460					PMID 33251049
	miR-19a	PMID 27991929				
	miR-20a			PMID 30631060		
The YAP sub-network	YAP			PMID 28356122		
The miR-24 sub-network	miR-24			PMID 28500171		
The LINC00152 sub-network	LINC00152					PMID 27633443
The miR-27a sub-network	miR-27a				PMID 26913599	
The miR-31 sub-network	miR-31	PMID 28870287				

EZH2/UCA1 network is the main component of the metastasis network in CRC. The common target of multiple ncRNAs in this network was the oncogene EZH2 (enhancer of zeste2 polycomb repressive complex 2 subunits). The histone lysine N-methyltransferase encoded by the EZH2 gene is an important part of the PRC2/EED-EZH2 complex, which can methylate the "Lys-9" (H3K9me) and "Lys-27" (H3K27me) of histone H3 and inhibits the transcription of its downstream target genes (McCabe et al., 2012; Hübner et al., 2019). Mutation or over-expression of EZH2 is associated with many types of cancers (breast cancer, prostate cancer, melanoma, bladder cancer, etc.) (Bracken et al., 2003). Presently, many EZH2 targets have been identified. For example, the INK4B-ARF-INK4A tumor suppressor gene locus is a well-known target of EZH2 and its inhibition affects cancer growth and embryonic development (Kheradmand Kia et al., 2009); E-cadherin gene is another critical target of EZH2, and its down-regulation is essential for EMT and metastasis (Luo et al., 2016). Mu Xu et al. report that lncRNA SNHG6 acts as a molecular sponge of miR-26a/b and miR-214, and releases EZH2 by isolating the endogenous microRNA of CRC cells, which mainly regulates the expression of EZH2 in CRC (Xu et al., 2019a). Moreover, EZH2 and its targets H3K27me3, P14ARF, P15INK4b, P16INK4a and E-cadherin are involved in the carcinogenic effect of SNHG6 in CRC and regulate the EMT (Xu et al., 2019a).

In the sub-network of EZH2, O-glycosylation, is a unique post-translational modification (PTM), which participates in CRC metabolic reprogramming. The level of O-glycosylation increases in metastatic CRC tissues or cells. The expression of miR-101 reduces, while the expression of o-GlcNAc acyltransferase (OGT) and EZH2, which are regulated by miR-101, increases significantly. The down-regulation of miR-101 promotes O-GlcNAcylation, and the increased O-GlcNAcylation further enhances the stability and function of the EZH2 protein. O-GlcNAcylation and EZH2-mediated H3K27me3 modification of the miR-101 promoter region further reduce the expression of miR-101, consequently, miR-101/O-GlcNAcylation/EZH2 signals form a feedback loop that inhibits metastasis and eventually inhibits the invasion of CRC cells and regulate the EMT (Jiang et al., 2019). Thus, EZH2 has extremely high potential as a new target for CRC treatment.

Another important network node in the network diagram was CRNDE. CRNDE is located on human chromosome 16 and is highly expressed in a variety of cancers including CRC. CRNDE binds to EZH2, which in turn, can directly bind to DUSP5 and CDKN1A promoter regions, and induce histone H3 lysine 27 trimethylation (H3K27me3) modification in DLD1 and HCT116 cells (Ding et al., 2017a). This also inhibits dual specific phosphatase 5 (DUSP5) and CDKN1A expression and promotes the development of CRC (Ding et al., 2017a). In addition, CRNDE is also related to microRNAs. Han et al. found that miR-181a-5p could be used as the inhibitory target of CRNDE. β-catenin and TCF4 are inhibitory targets of miR-181a-5p and repress the Wnt/β-catenin signaling pathway. In CRC cell lines, CRNDE promotes CRC cell proliferation and chemotherapy resistance through the Wnt/β-catenin signaling pathway mediated by miR-181a-5p (Han et al., 2017). Thus, it warrants further studies to investigate the regulatory mechanism of CRNDE as a potential target in the therapy strategy and resistance of CRC.

Another ncRNA in the network diagram was the lncRNAs UCA1 (urothelial cancer associated 1). The presence of UCA1 in exosomes is verified, but its role and clinical applicability in CRC remain unclear. Barbagallo reported that UCA1 is upregulated in CRC biopsy (Barbagallo et al., 2018). In serum exosomes, the expression of UCA1 is regulated by an activating MAPK signal. UCA1 isolates miR-135a, miR-143, miR-214, and miR-1271 to protect ANLN, BIRC5, IPO7, KIF2A, KIF23 and other actin and cytoskeleton related proteins from miRNA-induced degradation, and thus, regulates their expression and promotes the progression of CRC and other key biological processes (Barbagallo et al., 2018). Luan et al. also demonstrate that UCA1 is upregulated in the serum exosomes of patients with CRC. UCA1 is packaged into exosomes which are transferred to CRC cells. As a ceRNA, UCA1 regulates the expression of MYO6 through miR-143, enhances cell proliferation and migration, and exerts essential functions in the tumor progression of CRC (Luan et al., 2020). Taken together, these reports suggest that UCA1 may be a potential new clinical biomarker for CRC.

From **Figure 4**, we observe that in addition to the CRNDE/EZH2/miR214/UCA1 network, the YAP sub-network and the miR-24 sub-network also play indispensable roles during the metastasis of CRC. YAP1 is upregulated through a variety of biological mechanisms and has a carcinogenic effect in a variety of tumors. As the core sub-network of CRC metastasis, YAP connected multiple ncRNAs such as GAS5, miR375, and circ1662, etc. The inactivation of YAP1 is required in cell-cell contact inhibition and act as a transcriptional co-activator to mediate the biological functions of the Hippo pathway (Zhao et al., 2007). It should be noted that lncRNA GAS5 (growth arrest-specific 5), a tumor suppressor in CRC as a ceRNA of miR-222-3p, regulates the expression of Beclin1, LC3B, and PTEN by targeting miR-222-3p/GAS5 phosphatase and PTEN signaling pathways, thereby inhibiting CRC cell migration and invasion, and promotes autophagy (Liu et al., 2019a). Notably, GAS5 as well as its target YAP are intently linked to m^6A modification. GAS5 directly interacts with the WW domain of YAP to promote the transfer of endogenous YAP from the nucleus to the cytoplasm, as well as its phosphorylation and its subsequent ubiquitin-mediated degradation which leads to tumor suppression (Ni et al., 2019). Interestingly, YTHDF3 selectively bound to GAS5 which was modified by m^6A and promoted the degradation of GAS5 in an m^6A-dependent manner. Meanwhile, GAS5 negatively regulated the expression of YAP, and YAP could bind to the promoter region of YTHDF3 to promote the transcription of YTHDF3, in other words, YTHDF3-GAS5-YAP-YTHDF3 formed a positive feedback loop and promoted the metastasis of CRC in an m^6A-dependent manner (Ni et al., 2019). Moreover, YAP not only regulated the expression of YTHDF3, m^6A modified YAP also directly bound to IGF2BP2, and stabilized YAP promoted the occurrence of CRC by up-regulating the expression of ErbB2 (Cui et al., 2021). In addition to directly regulating the expression of YAP mRNA, m^6A modification is supposed to indirectly regulate the expression of YAP1 protein. Chen et al. illustrated that the overexpression of METTL14 increased the m^6A level of primiR-375, and the m^6A-modified primiR-375 was transformed into premiR-375 under the action of DGCR8, thereby promoting the expression of miR-375 in CRC. Thereafter, elevated miR-375 suppressed the expression of YAP1, and ultimately inhibited the metastasis of CRC (Chen et al., 2020a). Interestingly, the expression of YAP1 protein is not only regulated by m^6A-modified miRNA, but also by m^6A-modified circRNA. Studies have shown that METTL3 induced the expression of circ1662 by installing m^6A modification in the circ1662 flanking reverse complement sequence. The overexpression of circ1662 promoted the transport of YAP1 protein to the nucleus and reduced the level of YAP1 protein in the cytoplasm and ultimately accelerated the metastasis of CRC (59).

MiR-590-5p inhibits the YAP expression by directly targeting its 3′UTR, thereby inhibiting intestinal inflammation and tumorigenesis of CRC cells (60). Ou et al., also validated the existence of the miR-590-5p/YAP axis. MiR-590-5p is a miRNA with density-sensitive property. The high density of CRC cells upregulates the expression of the RNase III endonuclease DICER1, which in turn promotes the biosynthesis of miR-590-5p and ultimately inhibits YAP expression (Ou et al., 2018). This also suggests that the miR-590-5p/YAP axis may be an important specific therapeutic target contributing to the pathogenesis of CRC. Furthermore, miR-590-5p itself may also serve as a therapeutic potential target for CRC patients. miR-590-5p is a hypoxia-sensitive miRNA and inhibits the expression of RECK, which promotes the invasion and metastasis of CRC cells by activating matrix metalloproteinases (MMPs) and filamentous processes in vitro, and consequently promotes tumor cell proliferation (Kim et al., 2019a). Moreover, Nuclear factor 90 (NF90), a direct target of miR-590-5p, is a positive regulator of vascular endothelial growth factor (VEGF) mRNA stability and protein synthesis. The NF90/VEGFA signaling axis can inhibit angiogenesis and metastasis in CRC (Zhou et al., 2016). In contrast, MiR-195, in the YAP sub-network, is an inhibitor of the Hippo-YAP signaling pathway. There are two conserved miR-195-5p homologous sites at the 3′UTR of YAP mRNA. MiR-195-5p inhibits EMT and blocks Hippo signaling, thereby inhibiting the proliferation, migration, invasion and epithelial-mesenchymal transition (EMT) of CRC cells (Sun et al., 2017). In addition, miR-195-5p can also regulate the expression of NOTCH2 in a post-transcriptional manner (Lin et al., 2019a).

Previous publications show that the miRNAs are usually organized in clusters (within 3 kb) in the genome and have the characteristics of a regulatory network that controls tumor metabolism. MiRNA clusters play essential roles in tumor progression by coordinating or inhibiting multiple target genes. The coordinated regulation of miRNA clusters may cause rapid switching of the metabolic signaling networks in CRC cells. Jin et al. report a cluster consisting of miR-23a, miR-27a and miR-24 induced by hypoxia conditions in CRC cells, which promotes glycolysis by regulating the related gene networks. Inhibition of miR-23a, miR-24, and miR-27a under hypoxic conditions weaken the stimulating effect of reduced oxygen on glycolysis-related genes along with the inhibitory effect on tricarboxylic acid cycle-related genes including PDHB, PDHA1, IDH2, DLD, and IDH3A. Moreover, miR-24 promotes the expression of HIF-1α by targeting VHL, forming a

double negative feedback loop and exhibits the strongest regulatory effect. Thus, it shows that the miR-23a/27a/24 cluster promotes the progression of CRC through metabolism reprogramming (Jin et al., 2019).

Other Sub-network in Colorectal Cancer

Among other sub-networks, miR-149/150-5p/LINC00460/miR-19a/20a occupies a major position. It covers tumorigenesis, metastasis and chemotherapy resistance of CRC. In the sub-network, LINC00460, acting as a vital ncRNA, linked multiple miRNAs such as miR-149-5p, miR-150-5p, etc. Studies show that LINC00460 has a carcinogenic effect on CRC. It recruits EZH2 (enhancer of zeste homolog 2, EZH2) and H3K27me3 to the tumor suppressor KLF2 promoter in the nucleus. Thereby, it epigenetically inhibits the expression and inactivation of KLF2 (Lian et al., 2018). LINC00460, as a molecular sponge of miR-149-5p, antagonizes its ability to inhibit the translation of cullin4A (CUL4A) protein and regulates the occurrence of CRC. Thereafter, LINC00460 directly interacted with IGF2BP2 and DHX9 and combined with m^{6}A-modified HGMA1 mRNA to enhance the stability of HGMA1 and ultimately promoted the metastasis of CRC (Hou et al., 2021). Notably, LINC00460 may also be a promising therapeutic target involved in chemotherapeutic resistance of CRC. Meng et al. found that LINC00460-miR-149/150-5p-mutant p53 feedback loop is associated with oxaliplatin resistance of CRC. Similarly, LINC00460 promotes oxaliplatin resistance by isolating miR-149-5p/miR-150-5p and upregulating the expression of the target p53 (Meng et al., 2020). In addition to LINC00460, the circCTNNA1 also acts as a ceRNA competitive sponging miR-149-5p to counteract its inhibitory effect on the downstream target FOXM1, thereby promoting the progression of CRC (Chen et al., 2020b). Similarly, circ5615 binds to miR-149-5p, exerting miR-149-5p sponge effect, upregulating TNKS, and subsequently promoting the progression of CRC through the Wnt/β-catenin signaling pathway (Ma et al., 2020). Thus, the carcinogenic functions of LINC00460 or circCTNNA1 as ceRNA in CRC were validated, which suggested that these indicators might be potential and valuable therapeutic targets in CRC treatment and multi-drug resistance.

Besides miR-149-5p, miR-150-5p, miR-19a/20 as critical parts of the sub-network, miR-200 family including miR-200, miR-200b-3p, and miR-200c-3p was found involved in the regulation of ZEB1 and XIST, etc. Interestingly, ZEB1 acted as one of the downstream targets of miR-200b-3p, the combination of XIST and miR-200b-3p disrupts the combination of miR-200b-3p and ZEB1. Meanwhile, XIST can also act as a sponge of miR-200b-3p to promote the expression of ZEB1 and thus promote the progression and metastasis of CRC (71). Importantly, recent report supports that METTL14 can increase the m^{6}A level of XIST and decrease the expression of XIST in a YTHDF2-dependent regulation manner. The decrease of XIST expression promotes the expression of miR-200b-3p by directly binding to miR-200b-3p (Yang et al., 2020a). Thus, these findings indicated that linking m^{6}A-modified XIST with miR-200 and miR-200c-3p might provide novel directions and approach for excavating the potential targets for CRC therapy.

Notably, another lncRNA, ZFAS1 is highly expressed in CRC tissues and cells. Moreover, as a miR-150-5p sponge, it targets and regulates the expression of its downstream VEGFA, and promotes the progression of CRC by promoting miR150-5p-mediated VEGFA/VEGFR2/Akt/mTOR signaling pathway and EMT (Chen et al., 2018). In addition, studies show that ZFAS1 promotes CRC by small nucleolar RNA-mediated 2′-O methylation through NOP58 recruitment and plays essential roles through the ZFAS1-NOP58-SNORD12C/78-EIF4A3/LAMC2 signaling axis (Wu et al., 2020b). Collectively, these researches broaden our spectrum and lay a solid foundation for further excavating the crosstalk functions between epigenetic modification and ncRNAs during the early prediction and therapy of CRC.

CONCLUSIONS AND PERSPECTIVES

During the past few decades, extensive promotions have been made to explore the biological functions of ncRNAs in the involvement of tumorigenesis and progression of various types of tumors including CRC. In this review, we analyzed the regulation network and sub-networks related to ncRNAs involved in the progression, metastasis and chemoresistance of CRC via transcriptional and post-transcriptional epigenetic modification levels. Among the networks, the miR-34a/b/c/miR-194-5p/miR21 sub-network showed a direct relationship with oxaliplatin resistance for CRC therapy. Meanwhile, the CRNDE/EZH2/UCA1 sub-network had a significant association with metastasis and progression of CRC. Furthermore, we analyzed the regulatory manner of the core m^{6}A regulators with m^{6}A-related ncRNAs as exemplified by YTHDF3-GAS5-YAP, IGF2BP2-YAP-ErbB2, METTL14-YTHDF2-XIST, MeCP2/METTL14-KLF4, LINC00460/IGF2BP2/DHX9-HMGA1 signaling axis in CRC progression.

Thus, the crosstalk and regulation network of m^{6}A modifications associated modulators and ncRNAs provide a novel direction for exploring the underlying regulatory mechanisms of gene expression in CRC development.

Until now, multiple ncRNAs associated epigenetic m^{6}A modification modulators has been found acting as potential biomarkers and targets for CRC therapeutic interventions. However, these indicators have not been effectively developed and applied for the CRC therapy, partly due to exceeding targets for each regulator. For example, IGF2BP1, IGF2BP2 and IGF2BP3 has an enrichment of 3747, 3211, and 3914 high confidence downstream targets, respectively (Huang et al., 2018a). These targets and cellular biological pathways were closely connected to form a huge ncRNAs regulatory network. Thus, targeting multiple dysregulated targets in the m^{6}A associated ncRNAs network holds an important potential direction contributing for CRC therapy. Developing highly specific and selective small-molecule inhibitors targeting m^{6}A regulators and associated ncRNAs demand urgently for inter-individual precision therapy of CRC. Overall, the regulatory network provides a foundation for further study of ncRNAs, which also provide critical possibilities for clinical treatment

through their associations with m^6A epigenetic modifications that warrants further investigations for CRC.

AUTHOR CONTRIBUTIONS

XD and HW contributed to the conception of this study. XD and SL drafted the manuscript. XD, SL, XH and TS made the diagrams and tables. XD, SL and YW conducted literature screening and data collection. HW, XW, MW and SL revised the manuscript. All authors read and approved the final manuscript.

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