Non-Coding RNAs Regulate the Resistance to Anti-EGFR Therapy in Colorectal Cancer

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Colorectal cancer (CRC) is the third prevalent cancer worldwide, the morbidity and mortality of which have been increasing in recent years. As molecular targeting agents, anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (McAbs) have significantly increased the progression-free survival (PFS) and overall survival (OS) of metastatic CRC (mCRC) patients. Nevertheless, most patients are eventually resistant to anti-EGFR McAbs. With the intensive study of the mechanism of anti-EGFR drug resistance, a variety of biomarkers and pathways have been found to participate in CRC resistance to anti-EGFR therapy. More and more studies have implicated non-coding RNAs (ncRNAs) primarily including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), are widely involved in tumorigenesis and tumor progression. They function as essential regulators controlling the expression and function of oncogenes. Increasing data have shown ncRNAs affect the resistance of molecular targeted drugs in CRC including anti-EGFR McAbs. In this paper, we have reviewed the advance in mechanisms of ncRNAs in regulating anti-EGFR McAbs therapy resistance in CRC. It provides insight into exploring ncRNAs as new molecular targets and prognostic markers for CRC.

Keywords: miRNA, lncRNA, circRNA, CRC, EGFR, drug resistance

INTRODUCTION

CRC is the third most frequent cancer worldwide. Global cancer statistics in 2020 has shown there are about 1.932 million new cases and 935,000 deaths of CRC worldwide, accounting for 10.0% of the total new cases of cancer and 9.4% of the total cancer-related deaths, respectively (1). Following lung cancer, CRC causes the second highest mortality in cancer patients worldwide (1). The therapeutic strategies for CRC mainly include surgery, chemotherapy, radiotherapy and targeted therapy. Currently, surgery and chemotherapy are still the preferred treatment options for CRC. Nevertheless, patients with metastatic CRC (mCRC) have a poor prognosis (2). The combined chemotherapeutic and molecular targeted drugs can noticeably increase the progression-free survival (PFS) and overall survival (OS) of mCRC patients (3). As molecular targeted drugs, cetuximab and panitumumab can directly target epidermal growth factor receptor (EGFR). Combined with chemotherapeutic drugs, they are applied to effectively treat...
mCRC patients carrying wild-type *RAS* and *BRAF* (4). Unfortunately, few patients with mCRC are sensitive to anti-EGFR treatment, and most responding patients usually develop resistance to the therapy (5). In recent years, a variety of biomarkers and pathways have been found to participate in regulating the resistance to anti-EGFR therapy, and thus affecting the therapeutic effect and reducing the survival rate of CRC patients (6). Some studies have suggested the potential resistance mechanisms in order to explore strategies for overcoming anti-EGFR resistance (5, 7, 8) (Figure 1).

EGFR is a kind of HER tyrosine kinase receptor, which is composed of extracellular ligand binding domain, transmembrane hydrophobic domain, and intracellular tyrosine kinase domain. EGFR is selectively activated by binding to epidermal growth factor (EGF) as one of the major ligands. EGFR transmits signals from cytoplasm to nucleus through RAS/RAF/MEK/ERK/MAPK, PI3K/PTEN/AKT/mTOR, and some other intracellular signaling pathways which participate in regulating cancer cell proliferation, invasion, and angiogenesis (9). Abnormal expression and activation of any signal molecules mentioned above may lead to primary (de novo) or acquired (secondary) resistance to anti-EGFR therapy in mCRC (5). Abnormal EGFR gene copy number, protein expression of EGFR ligands, HER2 and MET gene amplifications, and activation of EGFR downstream cascade signaling pathways [including the mutations of RAS/BRAF/PIK3CA, the loss of PTEN, STAT3 phosphorylation, and epithelial-mesenchymal transition (EMT)], have been demonstrated to be associated with the primary resistance to anti-EGFR therapy in CRC (5, 7, 8). It has been well documented that the acquired resistance is attributed to EGFR ectodomain mutation (S492R), genetic alterations in RAS/RAF and other downstream signaling molecules, and the activation of intracellular signaling pathways that are bypassing EGFR and mediated by IGF1R, HER2, MET, and VEGFR (5, 7, 8). Multiple genetic and nongenetic mechanisms drive resistance to anti-EGFR therapy in CRC, with a significant overlap in primary and acquired resistance (8) (Figure 1).

ncRNAs are a type of RNAs which have no protein-coding function. According to the length, they are divided into two classes: small non-coding RNAs (sncRNAs) with a length of 18-200 nt, and long noncoding RNAs (lncRNAs) with a length over 200 nt. ncRNAs are widely involved in cell proliferation, apoptosis, autophagy, EMT, and cell cycle progression (10–14). Accumulated studies have suggested ncRNAs play important roles in tumorigenesis, progression, and anti-EGFR monoclonal antibodies (McAbs) treatment resistance in CRC (15–21). In this review, we have focused on current progress in the underlying molecular mechanisms of ncRNAs in regulating the resistance to anti-EGFR therapy in CRC. We aim to fully explore the potentials of ncRNAs as novel molecular targets and prognostic markers for CRC.

**FIGURE 1** | Mechanisms of anti-EGFR drug resistance in CRC. (A) Primary resistance mechanisms. (B) Acquired resistance mechanisms.
**MIRNAS**

**Biological Functions of MiRNAs**

MiRNAs are single-stranded small ncRNAs with a length of 21-25 nt. The synthesis of miRNAs involves multiple biological steps. Firstly, primary miRNAs (pri-miRNAs) are encoded by DNA in the nucleus and transcribed by ribonucleic acid polymerase II. Secondly, long pri-miRNAs are processed by ribonuclease III Drosha, which produces precursor miRNAs (pre-miRNAs) with a length of 60-70 nt. Lastly, pre-miRNAs are cleaved into mature double-stranded miRNAs by ribonuclease III Dicer in the cytoplasm. Then, mature miRNAs participate in forming RNA-induced silencing complex (RISC) (22). MiRNAs induce messenger RNA (mRNA) degradation and translation repression by directly binding to the 3'-untranslated region (3'-UTR) of targeted mRNAs, and act as regulators at the post-transcriptional level during gene expression process (23). They are widely involved in cell proliferation, apoptosis, autophagy, and immune response (10, 11, 18, 21).

Accumulated studies have suggested miRNAs participate in the pathogenesis of various diseases including cancers (24–28). MiRNAs act either as oncogenic miRNAs (onco-miRs) or tumor suppressive miRNAs (TS-miRs) with significant tissue- and organ-specificity (29, 30). Many studies have also found that miRNAs participate in regulating the drug resistance in CRC (31, 32). It has been demonstrated miR-31 negatively regulates breast cancer invasion and metastasis (33). However, it negatively regulates the expression of tumor suppressors and thus exerts oncogenic effects in lung cancer (34). In CRC, miR-31 has been documented to promote cancer progression by activating RAS signaling pathway and hypoxia inducible factor 1α (HIF-1α), respectively (35, 36). Taken together, miR-31 is involved in tumor progression and metastasis by serving as a TS-miR or an onco-miR in different malignancies. The diverse roles of miR-31 in cancer may be attributed to different types of cancer cells, specific targets, and other complicated factors. Further research is required to reveal its specific functions in CRC.

MiRNAs, aberrantly expressed in tumor tissues and tumor cells, exert their tumor suppressive- and oncogenic-functions by regulating different targeted genes (Figure 2). When the expression levels of TS-miRs decrease, negative regulation on targeted genes weakens. Besides, increasing expression levels of onco-miRs promotes tumor development, metastasis, and drug resistance through down-regulating tumor suppressive genes.

**MiRNAs Regulate Drug Resistance of Anti-EGFR Therapy in CRC**

MiRNAs regulates anti-EGFR drug resistance by directly targeting tumor-related genes involved in EGFR-related signaling pathways in CRC. Abnormal expression of miRNAs is commonly observed in anti-EGFR treatment-resistant CRC cells. Recent studies have shown that miRNAs may predict the prognosis and drug therapeutic efficacy of CRC patients (37–39).

The latest studies regarding miRNAs and drug resistance to anti-EGFR therapy in CRC have been described in the following subsections and briefly summarized in Table 1.

**Impact of MiRNAs on EGFR Signaling Pathway**

EGFR signaling pathway has been confirmed to be aberrantly activated in multiple malignant tumors, which is associated with tumor progression and prognosis. Increasing evidence has implicated miRNAs participate in regulating EGFR signaling pathway and play vital roles in anti-EGFR drug resistance in CRC (Figure 2). Zhou et al. have found miR-133b regulated cell proliferation and invasion in CRC by targeting EGFR (40). Moreover, the combination of miR-133b mimics and cetuximab can effectively suppress the proliferation and invasion of cetuximab-resistant CRC cells (40). Suto et al. have found miR-7 is involved in regulating the EGFR signaling

![FIGURE 2 | Mechanisms of miRNAs regulating anti-EGFR drug resistance in CRC.](image-url)
pathway by down-regulating the expression of EGFR and RAF-1, which could inhibit CRC cells proliferation and reverse cetuximab resistance in CRC patients with mutant KRAS (41). Sun and the colleagues have found that miR-302a suppressed CRC metastasis by targeting nuclear factor I B (NFIB) and CD44 and decreasing the activation of NFIB/ITGA6 signaling pathway (42). MiR-302a has also been found to restore the response to cetuximab by inhibiting CD44-induced cancer stem cell (CSC)-like characteristics through EGFR-mediated MAPK and protein kinase B (AKT) signaling pathways (42). These studies have revealed that miRNAs can directly target EGFR (or RAF) in CRC cells, inhibit the activation of its downstream signaling pathways, and thus repress CRC cells growth and invasion. Besides, miR-100 and miR-125b have been found to cooperatively regulate the resistance to cetuximab in CRC through Wnt signaling pathway that has a cross-talk with EGFR pathway (50). MiRNAs are extensively involved in regulating the resistance to cetuximab. Accordingly, miRNAs might serve as markers for predicting anti-EGFR therapy in mCRC patients due to their regulatory effects on EGFR signaling pathway.

### Impact of miRNAs on RAS Signaling Pathway

KRAS, a member of RAS family, has almost 40% mutation rate in CRC patients. KRAS mutations are predictive biomarkers for the treatment efficacy of anti-EGFR treatment and the outcome of patients with CRC (53). MiRNAs have been widely reported to regulate the therapeutic response and drug sensitivity of CRC patients through KRAS signaling pathway (43–45) (Figure 2).

Synthetic miR-143 (miR-143#12) inhibits KRAS signaling pathway activation and restores the sensitivity of cetuximab-resistant CRC cells by targeting the KRAS activating protein SOS1 (43). Overexpression of miR-143 or miR-145 can increase the sensitivity to cetuximab by enhancing cetuximab-mediated antibody-dependent cellular cytotoxicity (ADCC) in CRC cells (44). Strippoli et al. have demonstrated miR-31-3p, miR-143 and miR-145 are closely correlated with anti-EGFR treatment resistance in mCRC via regulating RAS-MAPK axis and c-MYC pathway (45). Moreover, miR-143 and miR-145 have been well established to exert tumor-suppressive effects and are beneficial for the efficacy of anti-EGFR treatment in CRC, whereas miR-31-3p comes to the opposite. It has been shown that the overexpression of miR-193a-3p can promote BRAF-mutant CRC cells apoptosis by inhibiting the expression of KRAS and myeloid cell leukemia-1 (Mcl1) through MAPK signal (47). As a tumor suppressor, miR-193a-3p promotes the efficacy of BRAF inhibitor dabrafenib (DAB) and MEK inhibitor trametinib (TRA), and enhances the anti-proliferative effect of combined therapy of DAB, TRA with cetuximab in CRC (47). A recent study has shown that 4-acetylethyl-octadec-2-ynol (4-AAQB) inhibits CRC cell proliferation and induces cell apoptosis by up-regulating miR-193a-3p, down-regulating KRAS and inhibiting the activation of KRAS signaling pathway. The combined treatment of 4-AAQB with cetuximab can make KRAS-mutant CRC cells resensitized to cetuximab (46). In addition to KRAS, miR-193a-3p acts on multiple signaling pathways and plays a tumor-suppressive role by regulating the expression of interleukin 17 receptor D (IL17RD) and erb-b2 receptor tyrosine kinase 4 (ERBB4) in CRC (54, 55). And lower expression of miR-193a-3p in CRC tissues predicts poorer PFS independently of the status of BRAF mutation (56). Accordingly, miR-193a-3p may serve as a prognostic biomarker. Its combination with molecular targeted drugs may be a novel therapeutic strategy for BRAF-mutant CRC. Weng et al. have reported that lauric acid can induce miR-378 expression and increase the sensitivity of BRAF- and KRAS-mutant CRC cells to cetuximab by inhibiting KRAS, BRAF, MEK, ERK1/2 protein expressions through the MAPK signaling pathway (48). In addition, they have found that eicosapentaenoic acid ethyl ester (EPA) can also increase the expression of miR-378 in BRAF- and KRAS-mutant CRC cells and resensitize KRAS-mutant CRC cells to cetuximab (49). Taken together, miRNAs play vital roles in regulating the therapeutic response and drug sensitivity of KRAS- or BRAF-mutant CRC through RAS signaling pathway. Potential miRNAs and key molecules in the RAS signaling pathway may serve as promising biomarkers for predicting the efficacy and drug resistance during the targeted therapy in CRC.

### TABLE 1 | MiRNAs involved in anti-EGFR drugs resistance in CRC.

| MiRNAs | Expression | Targets/Pathways | Drugs | References |
|--------|------------|-----------------|-------|------------|
| MR-133b | Down-regulated | EGFR pathway | Cetuximab | (40) |
| MR-7    | Down-regulated | EGFR/RAF pathway | Cetuximab | (41) |
| MR-302a | Down-regulated | CD44/EGFR/RAS/MAPK pathway, CD44/EGFR/Pi3K/AKT pathway | Cetuximab | (42) |
| MR-143  | Down-regulated | SOS1/RAS/ERK/MAPK pathway, AKT pathway | Cetuximab | (43) |
| ADCC    |            | RAS-MAPK axis, c-MYC pathway | Cetuximab | (44) |
| MR-145  | Down-regulated | ADCC | Cetuximab | (45) |
| MR-193a-3p | Down-regulated | KRAS/RAF/MEK/ERK pathway | Cetuximab | (46) |
| MiRNA   |            | Mcl1/EGFR/BRAF/MEK/MAPK pathway | Dabrafenib, Trametinib, Cetuximab | (47) |
| MiRNA   |            | ERK/MAPK pathway | Cetuximab | (48, 49) |
| MiRNA   |            | RAS-MAPK axis, E2F2/c-MYC pathway | Cetuximab | (50) |
| MiRNA   |            | DKK1, ZNF3/Wnt/β-catenin pathway | Cetuximab | (51) |
| MiRNA   |            | ZNF3, RNFL3, DKK3, APC2/Wnt/β-catenin pathway | Cetuximab | (52) |
| MiRNA   |            | PHLP1/AKT pathway | Cetuximab | (53) |
| MiRNA   |            | PHLP1/AKT pathway | Cetuximab | (54) |
| MiRNA   |            | CTGF/EGFR/Pi3KCA/AKT pathway, EGFR/KRAS/BRAF/ERK1/2 pathway | |

Chu et al. NcRNAs in CRC Drug Resistance

Figure 2

TABLE 1 | MiRNAs involved in anti-EGFR drugs resistance in CRC.
Impact of MiRNAs on PI3K/AKT Signaling Pathway

The PI3K/AKT signaling pathway is widely involved in carcinogenesis and cancer progression. Aberrant activation of PI3K-AKT can promote CRC invasion and metastasis (57). It has been reported that miRNAs can directly target the PI3K/AKT signaling molecules or signaling pathway regulators, including numerous regulatory proteins (51, 52, 57–60) (Figure 2). MiR-375 and miR-199a-5p promote cetuximab resistance in CRC patients by repressing the expression of PH domain and leucine-rich repeat protein phosphatase 1 (PHLPP1) and positively regulating AKT signaling pathway (51). Nevertheless, some other studies have found miR-375 and miR-199a-5p inhibit CRC cells proliferation and invasion, suggesting their complicated functions in CRC (52, 58–60). It has been well documented that miR-375 suppressed CRC cell proliferation by targeting PIK3CA via the PI3K/AKT pathway (61), while miR-199a-5p inhibited CRC cell survival, proliferation, migration, and invasion by downregulating GCNT2 expression and inhibiting the AKT and ERK signal activation (62). Different roles of miR-375 and miR-199a-5p exerting in CRC, might be attributed to significant tumor heterogeneity among patients. Taken together, miRNAs regulate the progression and drug resistance of CRC by regulating tumor suppressors or oncogenes involved in various signaling pathways including PI3K/AKT signal. However, the precise mechanisms of miR-375 and miR-199a-5p underlying the resistance to anti-EGFR drugs in CRC warrant to be fully elucidated in more future research.

Impact of MiRNAs on Tumor Immune Microenvironment

Tumor immune microenvironment is composed of a variety of cells, extracellular matrix and various signaling molecules (63). Imbalance of tumor immune microenvironment is essential for tumor growth, metastasis and prognosis (64). MiRNA-mediated regulation of tumor microenvironment (TME) has been demonstrated to affect cancer growth, angiogenesis, metastasis, and drug resistance exerting either antitumor or tumorigenic effects (65). For instance, a recent study has shown miR-34a promoted the expression of B7-H3 and TNF-α in tumor microenvironment and negatively regulated T cell-mediated immune response, which thus induced immunosuppression and immune escape in CRC (66). MiR-148a-3p and miR-448 respectively down-regulate the expression of calcineurin (CAXN) and indoleamine 2,3-dioxygenase 1 (IDO1), which enhances CD8+ T cell-mediated immune response in CRC (67, 68).

Cetuximab can induce ADCC by binding to EGFR on cancer cells and CD16 receptor on natural killer (NK) cells and dendritic cells (DCs) (69–71). It stimulates the production of proinflammatory cytokines, such as IFN-γ and TNF-α, and activates cytotoxic T cells in the TME, thereby exerting tumor immunosuppressive effects (69–71). It has been suggested that anti-EGFR therapy and immunotherapy have synergistic and complementary mechanisms. The combination of immune checkpoint inhibitors, chemotherapy with anti-EGFR McAbs in mCRC has shown an encouraging clinical outcome (72). Nevertheless, littler is known about the role of miRNAs in regulating tumor immune microenvironment and thus affecting anti-EGFR drugs resistance in CRC.

LncRNAs

Biological Functions of LncRNAs

LncRNAs are a type of ncRNAs over 200 nt in length. They are mainly formed by RNA polymerase II-catalyzed transcription typically containing a cleavable 3’ poly-A tail (73). According to genomic localization, LncRNAs are grouped into five classes: sense lncRNA, antisense lncRNA, intronic lncRNA, bidirectional lncRNA, and intergenic lncRNA (74). LncRNAs have low sequence conservation and high tissue and organ specificity. As competitive endogenous RNAs (ceRNAs), LncRNAs can directly sponge miRNAs and inhibit their expression. LncRNAs interact with DNA, RNA and protein, acting as regulators of gene expression at multiple levels and play roles in various cell processes, such as genomic imprinting, epigenetic regulation, transcriptional regulation, chromosome conformation, and cell cycle regulation (75). A great deal of data has suggested LncRNAs participate in the pathogenesis of various diseases, including cancer (75–78). Linc00152, SNHG1, SCARN2, DLEU1 and XIST contribute to colorectal carcinogenesis, metastasis and prognosis of CRC (54, 79–83). In addition, a number of studies have implicated LncRNAs lead to associated with primary or acquired drug resistance in CRC, thereby reducing drug efficacy (84, 85). Nonetheless, the regulatory mechanisms of LncRNAs underlying anti-EGFR therapy resistance in CRC are not clear yet.

LncRNAs Regulate Drug Resistance of Anti-EGFR Therapy in CRC

Increasing evidence has supported that LncRNAs participate in regulating CRC resistance to anti-EGFR McAbs through multiple signaling pathways (Figure 3). The study by Peng et al. has found that down-regulation of POU5FIP4 in cetuximab-sensitive CRC cells can reduce their sensitivity in mCRC (86). LNC00973 and several other LncRNAs may be involved in cetuximab resistance by regulating glucose metabolism (87). Down-regulation of LNC00973 can improve cetuximab resistance in drug-resistant CRC cells (87). Lu et al. have elaborated that the overexpression of LncRNA MIR100HG-derived miR-100 and miR-125b promotes cetuximab resistance through Wnt/β-catenin pathway in CRC (50) (Tables 1, 2). Recent studies have reported that LncRNA CRART16 is up-regulated in CRC cells with secondary cetuximab-resistance. CRART16 contributes to cetuximab resistance in CRC by up-regulating ERBB3 through miR-371a-5p/MAPK signaling pathway (88). LncRNA HCG18 promotes cell proliferation, migration, and cetuximab resistance in CRC by up-regulating PD-L1 and down-regulating CD8+ T lymphocytes via sponging miR-20b-5p (89). Besides, the study by Yang et al. has shown the evidence that up-regulation of UCA1 in cetuximab-resistant CRC cells and the produced exosomes (90). Moreover, exosomal UCA1 is observed to cause drug resistance in cetuximab-sensitive CRC cells (90). Due to its non-invasive and relatively stable content in...
serum, exosomal UCA1 is hopefully used as a new biomarker for CRC in the future (Table 2).

Accumulated studies have suggested lncRNAs have been elucidated to serve as ceRNAs by sponging miRNAs, which subsequently regulates miRNAs-mediated anti-EGFR therapy resistance in CRC. In addition, lncRNAs play vital roles in CRC progression, metastasis, and drug resistance. These findings provide therapeutic targets and potential prognostic markers for CRC with regard to lncRNAs. Future studies are warranted to reveal the specific mechanism of lncRNAs involved in CRC progression, metastasis, and drug resistance.

CIRCRNAS

Biological Functions of CircRNAs

CircRNAs are novel covalently closed circular single-stranded ncRNAs discovered in recent years, mainly formed by exon reverse splicing of pre-mRNA. According to the sequence origin, circRNAs are grouped into exonic circRNAs, circular intronic RNAs, and exon-intron circRNAs (91). They exist stably in plasma, serum, saliva, and other body fluids, and are widely expressed in various types of cells with cell- and tissue-specificity (92, 93). Acting as ceRNAs, circRNAs can competitively bind with miRNAs and regulate gene expression via interacting with miRNAs or RNA-binding proteins (RBPs). They exert essential effects on the progression of multiple diseases including cancer (17, 94–99).

CircRNAs Regulate Drug Resistance in CRC

Increasing evidence has supported that circRNAs participate in regulating tumorigenesis and drug resistance of CRC (100, 101). Chen et al. have found that circ-PRKDC acted as a miR-375 sponge and targeted FOXM1, and enhanced CRC cells resistance to 5-fluorouracil (5-FU) through the Wnt/β-catenin signaling pathway (102) (Table 3, Figure 4). CircRNAs of circ_0007031, circ_0007006, and circ_0000504 have been found to be module 5-FU resistance of CRC cells by regulating AKT3 via the AKT signaling pathway, while circ_0048234 can sponge miR-671-5p in 5-FU-resistant CRC cells via the EGFR signaling pathway (103) (Table 3, Figure 4). ATP-binding cassette (ABC) transporters, such as ABCB1, ABCC1, and ABCG2, have been reported to play crucial roles in CRC drug resistance by increasing drug efflux out of cancer cells (105). Inhibition expression of ABC transporters is an effective approach to reverse drug resistance in cancer cells (105, 106). A number of ncRNAs have been demonstrated to be involved in regulating ABC transporters in drug-resistant cancer cells by regulating EGFR and its downstream signaling pathways (107, 108). Circ_0007031 has been documented to induce 5-FU resistance by modulating the expression of ABC transporter ABCC5 through miR-133b/ABCC5 axis in CRC (100). MiR-7 functions as a regulator of anti-EGFR therapy resistance in CRC. It has been shown that ciRS-7 regulated CRC cell growth and invasion by sponging miR-7 and upregulating EGFR and IGF-1R expression (109). Similarly, ciRS-7 can function as ceRNA for miR-7 to activate EGFR/RAF1/MAPK pathway in CRC (110). The study by Zeng et al. has reported circHIPK3 sponged miR-7 to upregulate the expression of several oncopgenes, such as FAK, IGF1R, EGFR, and YY1, through the PI3K/AKT and MEK/ERK signaling pathways that contributing to drug resistance in CRC (104). Additionally, inhibition of circHIPK3 can reverse the

### TABLE 2 | LncRNAs involved in anti-EGFR drugs resistance in CRC.

| LncRNAs  | Expression | Targets/Pathways | Drugs     | References |
|----------|------------|------------------|-----------|------------|
| POU5F1P4 | Down-regulated | EGFR pathway | Cetuximab | (86)       |
| LNC00973 | Up-regulated | /               | Cetuximab | (67)       |
| MI100H   | Up-regulated | MIR100/DKK1, ZNRF3/Wnt/β-catenin pathway, MIR-125b/ZNRF3, RNF43, DKK3, APC2/Wnt/β-catenin pathway | Cetuximab | (50)       |
| CRART16  | Up-regulated | MIR-371a-5p/ERBB3/MAPK pathway | Cetuximab | (88)       |
| HCG18    | Up-regulated | MIR-20b-5p/TPD-L1 | Cetuximab | (89)       |
| UCA1     | Up-regulated | /               | Cetuximab | (90)       |

/., unmentioned in the reference.
resistance to cetuximab by targeting miR-7 in CRC cells (104) (Figure 4). All these findings have provided novel insights into the understanding of drug resistance mechanisms regarding circRNAs. Nevertheless, more studies are warranted to estimating the involvement and mechanism of circRNAs in regulating the resistance to anti-EGFR therapy in CRC.

PERSPECTIVES

Drug resistance remains a major challenge for CRC treatment. The mechanisms underlying CRC resistance to anti-EGFR therapy are complicated. Increasing studies have shown that ncRNAs play crucial roles in regulating the resistance to anti-EGFR therapy in CRC, primarily including miRNAs, lncRNAs and circRNAs, which have been identified as either oncogenes or tumor suppressors (111). Currently available studies have supported ncRNAs participate in modulating anti-EGFR drug resistance based on miRNAs-mRNAs, lncRNAs-miRNAs-miRNAs, or circRNAs-miRNAs-miRNAs regulatory networks through the EGFR signaling pathway, RAS signaling pathway, and PI3K/AKT signaling pathway. Accordingly, ncRNAs may function as novel biomarkers in predicting the efficacy and resistance of anti-EGFR therapy in CRC. Nevertheless, the molecular mechanisms of ncRNAs involved in anti-EGFR therapy resistance still warrant to be further elucidated in CRC. Further studies need to focus on investigating new therapeutic strategies based on ncRNAs regulatory networks combing with anti-EGFR targeted therapy in CRC.

AUTHOR CONTRIBUTIONS

SY, DX, and JC wrote the draft and revised it. JC, XF, ZS, LG, WD, HL, XY, JD, LLZ, and LZ collected the data and designed the tables and figures. All authors read and approved the submitted version.

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