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Research progress review on long non-coding RNA in colorectal cancer

Minireview

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Colorectal cancer (CRC) is one of the most common malignancies globally, and the morbidity and mortality rates associated with it are among the highest around the world. Not even great advances in colorectal cancer diagnosis and treatment technologies have been able to increase the 5-year survival rate in this disease. Recidivation and metastasis are the main causes of death in CRC, although the underlying mechanism remains unknown. Long non-coding RNA (lncRNA) is a type of non-coding RNA that is greater than 200 nt in length. LncRNAs are involved in cell proliferation, apoptosis, metastasis, and differentiation. Abnormal expression of lncRNAs is reported in various diseases. Relevant studies have demonstrated that lncRNAs are capable of interacting with DNAs, RNAs, and proteins, thereby regulating the Wnt, p53, and other signaling pathways and playing an important role in the biogenesis, progression, metastasis, and drug resistance in CRC. In the present report, recent progress in the research related to lncRNAs in colorectal cancer is reviewed.

Key words: lncRNA colorectal cancer, diagnosis and prognosis, biomarkers, drug resistance

Colorectal cancer is one of the most common malignancies worldwide that currently ranks third in incidence and second in cancer-related mortality [1]. In China, CRC ranks third in the incidence of malignant tumors and fifth in mortality rate [2]. Moreover, compared with European and American countries, CRC morbidity is significantly higher in males than in females and demonstrates a younger trend. In addition, the newly diagnosed cases of rectal cancer, middle, and lower rectal cancers, and young patients with CRC have been increasing annually [3], posing a serious threat to human health and creating a heavy burden on society. Despite the improvement in patient prognosis due to advances in the early diagnostic techniques and treatment for CRC, approximately 60% of the patients who seek medical advice have been reported to be associated with distant metastasis. Moreover, most of the patients who underwent surgery for CRC, unfortunately, presented with relapse and metastasis shortly after the surgery, and the 5-year survival rate of stage IV patients was less than 10% [4]. Therefore, it is imperative to improve the rate of early diagnosis and identify a suitable therapeutic target for CRC.

Advances in sequencing technology and genomics research over the years have revealed that only 1% to 2% of genes in the whole genome encodes proteins, whereas the majority of the remaining genes are transcribed as non-coding RNAs. Long non-coding RNAs (lncRNAs) are a type of non-coding RNAs that are greater than 200 nucleotides in length. LncRNAs interact with different biological macromolecules (DNA, chromatin, and proteins) and RNAs (mRNAs, miRNAs, and other lncRNAs) and play significant roles in various biological functions such as chromosome dosage compensation [5], epigenetic regulation [6], imprinting, nuclear and cytoplasmic transport, splicing, transcription, translation, cell cycle regulation, and cell differentiation [7, 8]. The majority of lncRNAs are located in the nucleus or cytoplasm, and their location within the cell determines their function [9]. LncRNAs located in the nucleus often interact with DNA, chromatin, transcription factors, chromatin regulatory factors, splicing bodies, and other nuclear proteins for transcription and epigenetic regulation [10], whereas those in the cytoplasm are involved mainly in the post-transcriptional, translational, and post-

translational regulation via epigenetic modifications and signaling pathways [11]. Several studies have demonstrated dysregulation of multiple lncRNAs, capable of activating or inhibiting metastasis in CRC, thereby promoting or inhibiting tumor development. In addition, lncRNAs regulate signaling pathways, such as PI3K/AKT, NF-κB, and CAMP, and ceRNAs, leading to drug resistance and reduced efficacy of fluorouracil (FU), oxaliplatin (OXA), and other drugs [12–14]. To generate novel ideas for the early diagnosis and treatment of CRC, we reviewed the studies concerning the impact of lncRNAs on the occurrence, development, metastasis, and drug resistance in CRC.

Types of lncRNAs and their functions

LncRNA is a type of non-coding RNA with a length greater than 200 nucleotides, no open reading frames (ORFs) and/or conservative codons, and no protein-coding sequences [15]. Compared to protein-encoding mRNAs, lncRNAs are more abundantly present with lower interspecific conservation and expression. According to several studies, certain lncRNAs encode small peptides and also translate into proteins greater than 50 amino acids in length [16, 17].

Types of lncRNAs. Based on genomic origin and relative positions of neighboring protein-encoding genes, lncRNAs are categorized into the following types [18–20]: sense lncRNAs that overlap with one or more exons of a coding gene; antisense lncRNAs that partially or completely complement the transcription product on the opposite chain; intronic lncRNAs that are produced from an intron; bidirectional lncRNAs that share a promoter with a protein-coding gene, whereas the transcription direction is opposite to that of the coding gene; intergenic lncRNAs (lincRNA) that are independently transcribed from the sequences located between protein-coding genes; enhancer RNAs (eRNAs) that are produced from the enhancer regions of protein-coding genes; and circRNAs that are covalently closed circular RNAs spliced from transcription products. Classification of lncRNAs is necessary to understand their functions, which are provided in the next section.

Functions of lncRNAs. Functions of lncRNAs are primarily based on their secondary structure that combines with proteins to enable chromatin remodeling and regulate the functions of transcription factors. In addition, lncRNAs affect the mRNA expression by acting as a "sponge" for adsorbing miRNAs, maintaining mRNA stability, and influencing the translation, shearing, and degradation of mRNAs by binding directly with the mRNA. To date, four categories of lncRNA functional modes have been identified: signaling – research has revealed specific transcription of lncRNAs under the effect of different stimulants and signaling pathways, and the participation of lncRNAs as signal transduction molecules in specific signaling pathways to regulate the transcription of downstream genes; lure: certain lncRNAs bind directly to RNA (ceRNAs)/proteins (transfer factors and transcription regulators), blocking the function of the latter and consequently the downstream signaling pathways, thereby regulating the transcription of the downstream gene; guidance: certain lncRNAs combine with transcription factors and locate the protein complex on specific DNA sequences, thereby affecting the transcription of downstream molecules similar to the action of a molecular chaperone; and molecular scaffolds: such lncRNAs perform a "central platform" role of combining multiple related transcription factors to exchange and integrate the information between different signaling pathways, allowing for rapid feedback and regulation of external signals and irritants. According to correlation research, similar to proteins, the expression of lncRNAs varies with the tissues and cells they are present in and regulated precisely. In addition to regulating normal physiological activities, lncRNAs play a significant role in the occurrence and development of several diseases, including colon cancer. Abnormal expression of lncRNAs is associated with proliferation, invasion, metastasis, and drug resistance in CRC [13, 21–23]. In contrast, stable expression of lncRNAs has been reported in peripheral blood, exosomes, plasma, and other tissues, which could be utilized as biomarkers for early diagnosis of CRC [24, 25].

LncRNAs as biomarkers for diagnosis and prognosis of colorectal cancer

Colon cancer-associated transcript 1. Colon cancer-associated transcript 1 (CCAT1), also known as CARLo-5, is located at chromosome position 8q24 in humans, a region containing several single nucleotide polypeptides (SNPs) associated with tumors [26], where the homozygosity of the G allele of rs6983267 augments the risk of diversified cancers [27, 28]. Nissan et al. [29] were the first to report in 2012 that the expression of CCAT1 in colon adenocarcinoma was 235 times higher than that in normal colon mucosa during the early-stage tumorigenesis, such as in adenomatous polyps, as well as in the proximal colonic epithelial mucosa of the tumor. The CCAT1 overexpression was detected in 40% of patients with CRC, whereas it was absent in the healthy controls. Kim et al. reported a frequently high CCAT1 expression in normal colon tissues of patients at high risk of CRC [30], resulting in high sensitivity and specificity of CCAT1. Zhao et al. [31] evaluated the clinical significance of peripheral blood CCAT1 as a biomarker for CRC and reported that the plasma levels of CCAT1 in patients with CRC were overtly higher compared with the healthy volunteers. According to the ROC curve analysis, plasma CCAT1 exhibited advanced diagnostic performance in CRC detection, with 75.7% sensitivity and 85.3% specificity. CCAT1 is a potential diagnostic biomarker for CRC and a therapeutic target of CRC-related lncRNAs.

Colon cancer-associated transcript 2. Colon cancer-associated transcript 2 (CCAT2) is also located at chromosome position 8q24 in humans. CCAT2 is overexpressed in

numerous tumor tissues, where it is involved in the proliferation, invasion, and metastasis of tumor cells [32–34]. The expression of CCAT2 is higher during chromosome instability and in microsatellite-stable (MSS) CRC tissues compared with normal mucosa lacking chromosome instability and microsatellite-unstable (MSI-H) CRC tissue. Furthermore, CCAT2 upregulates MYC, miR-17-5p, and miR-20a through TCF7L2-mediated transcription regulation, leading to increased activity of the Wnt signaling pathway [35]. In comparison with non-cancerous tissues, the colon cancer tissues, particularly the metastatic tissues, exhibit a significantly higher CCAT2 expression. Further, patients with high CCAT2 expression are more likely to present tumor recurrence and poorer clinical prognosis [36, 37]. Both serum and exosome levels of CCAT2 were distinctly higher in patients with CRC and preoperative specimens compared with healthy subjects and postoperative specimens, respectively, indicating that serum and exosome CCAT2 may serve as novel biomarkers for diagnosis of CRC [38].

Hepatocyte nuclear factor 1 alpha-antisense 1. HNF1A-AS1 is located at chromosome position 12q24.31 in humans and is expressed at abnormal levels in numerous tumors. The upregulation of HNF1A-AS1 has been reported in CRC [39], lung cancer [40], oral squamous cell carcinoma [41], bladder cancer [42], and liver cancer [43], where it promotes the proliferation, invasion, and metastasis of tumor cells. Two meta-analyses [44, 45] have independently demonstrated a close association of HNF1A-AS1 expression with histological grade, stage, lymph node metastasis, and distant metastasis. Dramatically lower disease-free survival (DFS) was reported in patients with high HNF1A-AS1 expression compared with patients with low HNF1A-AS1 expression, suggesting that the expression of HNF1A-AS1 could be utilized as a biomarker for poor prognosis in cancer. Fang et al. reported that HNF1A-AS1 regulated the expression of miR-34a via ceRNA, inhibited the miR-34a/SIRT1/p53 pathway, and activated the Wnt signaling pathway, thereby playing a significant oncogenic role and promoting metastasis in CRC, indicating that HNF1A-AS1 could serve as a prognostic marker and a potential therapeutic target for CRC [46].

Growth arrest-special transcript 5. Growth arrest-special transcript 5 (GAS5) is located at chromosome position 1q25.1 in humans and belongs to the tumor suppressor gene cDNA subtractive library. GAS5 is downregulated in various cancers and is closely associated with the clinicopathological features and prognosis of patients. GAS5 participates in cell proliferation, metastasis, invasion, apoptosis, and epithelial–mesenchymal transition (EMT) through a variety of molecular mechanisms [47–50]. Li et al. [51] detected 126 pairs of CRC tissues and their matched para-cancerous tissues and reported that the expression of GAS5 was distinctly lower in tumor tissues as compared with that in para-cancerous tissues and was closely related to tumor size and the clinical stage. In addition, the authors observed that GAS5 upregulation inhibited the proliferation, migration, and invasion of CRC cells by restraining the ALK/ERK pathway. The expression of GAS5 could serve as an independent prognostic factor. Liu et al. [52] monitored the levels of GAS5 in the tissues, plasma, and exosomes of 158 patients with CRC and 173 healthy subjects, and reported that the former exhibited significantly lower GAS5 expression than the latter. Huang et al. [53] measured the serum levels of GAS5 in 109 patients with CRC and 99 normal volunteers and discovered that the total serum GAS5 levels were significantly downregulated in patients with CRC compared with normal controls and were closely related to solid tumor volume and lymph node metastasis. Altogether, these results suggested that GAS5 was closely related to CRC and could serve as a biomarker for its screening.

HOX transcript antisense RNA. HOX transcript antisense RNA (HOTAIR), located at chromosome position 12q13.13 in humans, is an antisense RNA transcribed from the HOX locus. With a length of 2.2 kb, HOTAIR was the first identified lncRNA, exhibiting a trans-regulatory effect and regulating the expression of the HOXD gene [54]. In addition, HOTAIR interacts with PRC2 and recruits it to the target gene to mediate H3K27me3 and silence the gene. Chang et al. observed that HOTAIR interacted with histone demethylase LSD1/CoREST/REST complex and consequently regulated H3K4me2 and gene silencing [55]. Furthermore, HOTAIR promotes the proliferation, invasion, and metastasis of CRC cells via the miR26-mediated PI3K/AKT/mTOR pathway [56]. Ismail et al. [57] reported that HOTAIR expression in CRC patients with lymph node metastasis was significantly higher than that in those without metastasis. The levels of HOTAIR in the serum of patients with CRC were 7.55 higher as compared with those in the healthy volunteers. The sensitivity and specificity of HOTAIR expression in patients with CRC were 92.9% and 100%, respectively. Eighty-five percent of cases of early CRC could be detected by examining the levels of CCAT1 in the peripheral blood simultaneously [31]. Wang et al. [12] observed that HOTAIR promoted 5-FU resistance by inhibiting miR-218, consequently regulating VOPP1 expression and activating the NF-kB pathway in CRC. In contrast, HOTAIR knockdown reversed these effects. Moreover, HOTAIR suppressed the cytotoxic impact of 5-FU on CRC cells by promoting the expression of thymidylate synthetase. Among the 152 patients treated with 5-FU, the effective rate, overall survival (OS), and DFS of patients exhibiting high HOTAIR expression were distinctly lower compared with those with low HOTAIR expression. The Cox regression analysis revealed that HOTAIR levels served as an independent prognostic factor for OS in patients with CRC following 5-FU treatment.

Colorectal neoplasia differentially expressed. Colorectal neoplasia differentially expressed (CRNDE) is located at chromosome position 16q12.2 in humans and is upregulated in pancreatic cancer [58], gastric cancer [59], CRC [60], and breast cancer [61], where it promotes prolif-

eration and metastasis, interacts with chromatin-modified complex, and influences the epigenetic regulation of gene expression [62]. CRNDE has several alternative splicing variants, among which the most studied are CRNDE-h and CRNDE-p. Yu et al. [63] discovered that the expression of CRNDE-p in the serum and exosomes of 410 patients with CRC was higher than that in 58 patients with adenoma and 175 healthy people. In addition, the CRNDE-p expression was closely related to the clinical stage, tumor invasion depth, lymph node metastasis, and distant metastasis, and was observed to decrease significantly after chemotherapy in patients with CRC. Liu et al. [64] reported that the expression of CRNDE-h noticeably increased in the exosomes of patients with CRC in comparison with healthy volunteers. In addition, with a sensitivity of 70.3% and a specificity of 94.4%, CRNDE-h presented a better diagnostic value compared to CEA (carcinoembryonic antigen). The expression of CRNDE-h in the serum and tissues of patients with CRC highly correlated, whereas levels of CRNDE-h in the serum and exosomes of postoperative patients were significantly lower as compared with those in preoperative patients. Overall, CRNDE-p and CRNDE-h served as novel diagnostic biomarkers. Han et al. [65] reported that HCT116 and SW480 cells with downregulated CRNDE were more sensitive to 5-FU and OXA, whereas those with upregulated CRNDE were less sensitive to these two chemotherapy drugs. Moreover, chemoresistant HCT116 and SW480 cells displayed a marked increase in the expression of CRNDE. These findings suggested that CRNDE increased the resistance of CRC cells to chemotherapy drugs.

Nuclear-enriched abundant transcript 1. Nuclear-enriched abundant transcript 1 (NEAT1), located at chromosome position 11q65 in humans, is a 3.2 kb long non-coding RNA, which is enriched mainly in the nucleus and is crucial for the formation and maintenance of nuclear substructure paraspeckles. NEAT1 regulates gene expression in the nucleus, consequently impacting several pathophysiological processes [66, 67]. For instance, Yang et al. [68] reported that NEAT1 prevented DNA damage and maintained tumor cell proliferation and cell cycle in prostate cancer. Choudhry et al. [69] reported that NEAT1 promoted breast cancer cell proliferation and reduced apoptosis under the effect of HIF2 in hypoxic conditions and that high NEAT1 expression was associated with poor prognosis among the patients. The expression of NEAT1 is closely related to the TNM stage, low survival rate, and tumor recurrence in CRC, and therefore could serve as an independent prognostic factor for tumor recurrence [70]. Wang et al. observed that NEAT1 levels were higher in the tumor tissue as well as in the serum (ROC AUC = 0.9471) of 56 patients with CRC relative to healthy controls [71]. Because of the small sampling capacity, the use of NEAT1 as a diagnostic marker remains to be further explored, warranting multicenter studies with a larger sample size in the future. For summarization of the roles of all discussed lncRNAs see Table 1.

LncRNAs and drug resistance

With great advances in molecular biology techniques, anti-EGFR and anti-VEGF therapies have notably improved the effective rate and survival time of advanced CRC. However, chemotherapy continues to be the standard treatment for patients with CRC. Currently, FU, OXA, and irinotecan are commonly used drugs for chemotherapy. The overall response rate (ORR) of first-line chemotherapy is 40%, indicating that 60% of the patients are counteractive to chemotherapy. Several studies have reported that [72–74] the mechanism of drug resistance is interrelated with the expression of mRNAs and ncRNAs in the tumor tissue, with lncRNA the current focus.

LncRNAs related to fluorouracil resistance. Fluorouracil is one of the fundamental chemotherapy drugs used in CRC. Within cells, 5-FU is transformed through various mechanisms into effective fluorouracil deoxynucleotides, which subsequently interfere with DNA synthesis by blocking TS, ultimately leading to cell death. The ORR of 5-FU is approximately 50% when used alone or in combination for treating metastatic CRC, implying that nearly half of the patients exhibit resistance to 5-FU [75]. Although the resistance to 5-FU has been extensively studied, the underlying mechanism remains unknown.

Small nucleolar RNA host gene 15. Small nucleolar RNA host gene 15 (SNHG15), located at chromosome position 7p13 in humans, has a short half-life. Chen et al. [22] were the first to report the upregulation of SNHG15 in early gastric cancer, which is related to tumor progression. Subsequently, SNHG15 was reported to be overexpressed in liver cancer [76], breast cancer [77], and lung cancer [78], where it was associated with the prognosis of patients. Multiple studies have demonstrated that the increased expression of SNHG15 in CRC is related to liver metastasis, lymph node metastasis, TMN stage progression, and low overall survival rate (OSR). In addition, SNHG15 overexpression promotes cell migration and tumor growth *in vivo* and stabilizes Slug in colon cancer cells by inhibiting the ubiquitination and degradation of its zinc finger domain [79, 80]. Saeinasab et al. proposed SNHG15 as the carcinogenic lncRNA of CRC based on the results obtained by comparing the RNA-seq data of tumor tissues and adjacent normal tissues of 456 patients with CRC. Subsequently, it was reported that SNHG15 and MYC are co-expressed in CRC tissues and that MYC protein combines with two E-box motifs of the SNHG15 sequence, suggesting that MYC regulates the transcription of SNHG15. Knockdown of SNHG15 inhibited cell proliferation and invasion, reduced colony formation, and increased the sensitivity of cells to 5-FU, whereas its overexpression produced opposite effects. Functional studies have revealed significant differences in the expression of several genes associated with the function of apoptosis-inducing factors, including CTGF, GADD45A, GADD45B, HAS2, LAMC3, NRAS, BAG3, ERBB3, and CASP3. SNHG15 knockdown increased the

Table 1. Summarization of the roles of discussed lncRNAs in CRC.

LncRNA	Chromosome location	Dysregulation in CRC	Potential role and impact in CRC
CCAT1	8q24	↑	diagnostic biomarker and therapeutic target
CCAT2	8q24	↑	new biomarker for diagnosis
HNF1A-AS1	12q24.31	↑	prognostic marker and potential therapeutic target
GAS5	1q25.1	↓	biomarker for its screening
HOTAIR	12q13.13	↑	independent prognostic factor of OS after 5-FU treatment
CRNDE	16q12.2	↑	novel diagnostic biomarker and increases the resistance to chemotherapy drugs
NEAT1	11q65	↑	independent prognostic factor for tumor recurrence
SNHG15	7p13	↑	increases 5-FU resistance
HAND2-AS1	4q34.1	↓	enhances the sensitivity of 5-FU-resistant CRC cells to 5-FU
UCA1	19p13.12	↑	indicator of poor prognosis and increase the resistance to 5-FU
LINC00957	7p13	↑	induces 5-FU resistance
TUG1	22q12.2	↑in 5-FU resistant patients	induces 5-FU resistance
CASC15	6p22.3	↑	enhances resistance to OXA
LINC00152	2p11.2	↑	promotes L-OHP resistance
MIR100HG	11q24.1	↑in cetuximab resistant cell lines	maybe increase cetuximab resistance
KCNQ1OT1	11p15.5	↑	increases MTX resistance

Note: The sign '↑' stands for upregulation, and the sign'↓'stands for downregulation in tissues, serum or serum exosomes, and/or plasma of colorectal cancer patients; Abbreviations: CRC-colorectal cancer; 5-FU-fluorouracil; OXA/L-OHP-oxaliplatin; MTX-methotrexate; OS-overall survival

sensitivity of colorectal cells toward 5-FU [81]. This indicates that SNHG15 mediates the resistance of CRC cells to 5-FU by regulating the AIF activity, suggesting SNHG15 as a potential prognostic marker and target for RNA-based therapy.

Heart and neural crest derivatives expressed 2-antisense RNA 1. Heart and neural crest derivatives expressed 2-antisense RNA 1 (HAND2-AS1) is an antisense lncRNA located at chromosome position 4q34.1 in humans. It functions as an anti-oncogene in several tumors. For instance, low HAND2-AS1 expression in cervical cancer inhibits the proliferation, migration, and invasion of cell lines through negative regulation of ROCK1 in cervical cancer cells [82]. Downregulation of HAND2-AS1 in breast cancer is reported to be associated with poor clinical characteristics and prognosis in patients. In addition, HAND2-AS1 is reported to inhibit the proliferation and metastasis of breast cancer cells by regulating the expression of SOX7 via adsorption of mir-1275 [83]. Chen et al. [84] measured the expression of HAND2-AS1, miR-20a, and PDCD4 in tumor tissues and their matched para-carcinoma tissues in 50 patients with CRC (among whom 23 relapsed) receiving 5-FU-based chemotherapy, and reported the following results (in comparison with normal tissues): the levels of HAND2-AS1 and PDCD4 in patients with CRC were significantly lower; the miR-20a levels were significantly higher; the expression of HAND2-AS1 and PDCD4 in the relapse group was lower than that in the no-relapse group, whereas the expression of miR-20a was negatively correlated with the expression of HAND2-AS1 and PDCD4 in tumor tissues, and the PDCD4 expression was positively correlated with HAND2-AS1 expression. In addition, the OSR was markedly higher in patients with high HAND2-AS1 expression compared with those with low HAND2-AS1 expression. The overexpression of miR-20a and under-expression of HAND2-AS1 were also detected in HCT116/5-FU and SW480/5-FU cell lines. High HAND2-AS1 expression enhanced the sensitivity of 5-FU-resistant CRC cells to 5-FU, decreased the IC50 of HCT116/5-FU and SW480/5-FU cells, prominently reduced the levels of Bcl-2, MMP2, and MMP9, and promoted Bax expression. Studies exploring the underlying mechanism demonstrated that HAND2-AS1 enhanced the sensitivity of 5-FU-resistant CRC cells to 5-FU; inhibited the proliferation, migration, and invasion of cells; and promoted cell apoptosis by regulating PDCD4 expression via miR-20a adsorption.

Human urothelial carcinoma-associated 1. Human urothelial carcinoma-associated 1 (UCA1) is located at chromosome position 19p13.12 in humans. Initially, UCA1 was observed to be highly expressed in bladder metastatic cell carcinoma as three different transcripts of 1.4 kb, 2.3 kb, and 1,456 bp. It is now reported that UCA1 is highly expressed in multiple tumors [85–87], where it promotes the proliferation, invasion, and metastasis of tumor cells and inhibits apoptosis both *in vitro* and *in viv*o. A meta-analysis [88] of seven studies involving 775 patients with CRC revealed that UCA1 overexpression was associated with poor OS in patients with CRC (H = 2.25, 95% confidence interval [CI]: 1.77–2.87, p<0.001). High UCA1 levels were negatively correlated with tumor differentiation (odds ratio [OR]=2.84, 95% CI: 1.87–4.31, p<0.001), lymph node metastasis (OR=3.48, 95% CI: 2.24–5.41, p<0.001), distant metastasis (OR=2.67, 95% CI: 1.32–5.38, p=0.006), tumor invasion depth (OR=2.18, 95% CI: 1.03–4.61, p=0.04), and tumor size (OR=2.27, 95% CI: 1.56–3.32, p<0.001). It is suggested that UCA1 could serve as an indicator of poor prognosis in patients with CRC. Huang et al. [23] confirmed that patients with high UCA1 expression had a poor prognosis. COX

regression analysis indicated that UCA1 levels and distant metastasis were independent prognostic factors for patients with CRC. *In vitro* knockdown of UCA1 inhibited the growth of CRC cells and promoted 5-FU-induced apoptosis. When treated with different concentrations of 5-FU, the survival rate of CRC cells with UCA1 deletion was significantly reduced compared with the control group, whereas the opposite effect was observed in UCA1-overexpressed CRC cells, indicating that UCA1 increased the resistance of CRC cells to 5-FU. Studies exploring the underlying mechanism demonstrated that UCA1 adsorbed miR-204-5p and inhibited its endogenous activity, thereby regulating the protein expression downstream of CREB1 and inducing apoptosis to affect the sensitivity to 5-FU. Moreover, several studies have demonstrated that UCA1 increased cisplatin resistance in the bladder and ovarian cancers [89, 90]. UCA1 may induce non-T790M acquired resistance after EGFRTKI treatment in EGFR-mutant non-small cell lung cancer [91]. Altogether, these findings suggested that UCA1 played a significant role in chemoresistance.

*LINC00957***.** LINC00957, located at chromosome position 7p13 in humans, is a recently discovered lncRNA, which is rarely reported in the literature. Zhang et al. [92] analyzed the lincRNA expression profiles of 440 patients with CRC available in the TCGA database and observed that LINC00957 significantly correlated with patient survival. In a study involving 160 pairs of tumor tissues and their matched paracarcinoma tissues, LINC00957 expression was observed to be dramatically higher than that in the normal tissues, and it was closely related to the TNM stage and the efficacy of chemotherapy. Patients with CRC with high LINC00957 expression have a worse prognosis. Furthermore, the LINC00957 expression is higher in CRC cells compared with NCM460 (normal colorectal epithelial cells). This overexpression has also been detected in 5-FU-resistant cell lines. si-RNA-mediated silencing of LINC00957 in 5-FU-resistant cells dramatically reversed this resistance. A low-throughput screening of related drug-resistant genes revealed a downregulated transcription of ABCB1 gene and reduced P-gp expression. LINC00957 has been reported to be positively correlated with P-gp in terms of transcription and protein levels in tumor samples from patients with clinically ineffective 5-FU treatment. P-gp overexpression is one of the main mechanisms underlying the reduction in drug accumulation and the development of multi-drug resistance (MDR) in human MDR tumor cells [93], indicating that LINC00957 induces chemotherapy resistance through regulation of P-gp expression.

Taurine upregulated gene 1. Taurine upregulated gene1 (TUG1) is located at chromosome position 22q12.2 in humans. Initially, TUG1 was identified as a taurine upregulated transcript with a function related to retinal development [94]. The expression of TUG1 varies with the type of tumor. It is overexpressed in bladder cancer [95], gastric cancer [96], and cervical cancer [97], and downregulated in non-small cell lung cancer [98]. Wang et al. [99] detected the expression of TUG1 in 124 patients with CRC and subsequently observed that the expression of TUG1 in 42 patients with failed FU treatment was significantly higher than that in 42 patients without recurrence. Moreover, TUG1 levels are related to the depth of tumor invasion and the TNM stage. The risk of recurrence in patients with high TUG1 expression is notably higher compared with those with low TUG1 expression. *In vitro* studies have revealed a significantly higher IC50 for HCT8-5-FU-resistant cell line (HCT8FU) compared with the HCT8 cell line and a markedly higher TUG1 expression in the HCT8-5-FU cell line. After TUG1 knockdown, compared with the control group, the IC50 of HCT8-5-FU was reduced by 64.9%, the proliferation ability of cells significantly decreased, and the proportion of apoptosis was significantly increased. Furthermore, TUG1 knockdown significantly increased the level of miR-197-3p, a ceRNA regulated by TUG1, in CRC cells. The structure of miR-197-3p contains the binding site for thymic synthetase (TYMS) mRNA 3'UTR. TYMS is one of the pivotal enzymes in the 5-FU catabolic pathway, and patients with CRC and a low expression of this enzyme are more sensitive to 5-FU chemotherapy [100]. TUG1 downregulation restored the sensitivity to 5-FU in resistant cells, the overexpression of TYMS largely reversed the effect of TUG1 gene knockout. Therefore, it was concluded that TUG1 induced 5-FU resistance in CRC by inhibiting the miR-197-3p/TYMS axis. Thus, TUG1 inhibition could serve as a feasible treatment strategy to reverse 5-FU resistance.

LncRNAs related to oxaliplatin resistance. Oxaliplatin represents the third-generation of water-soluble platinum compounds. The covalent combination of platinum atoms in OXA with G on the DNA chain allows the formation of intrastrand and interstrand DNA cross-links as well as protein cross-links, thereby causing DNA damage, impairing DNA replication, and leading to apoptotic cell death. Oxaliplatin-based chemotherapy dramatically improved the treatment efficacy and increased the survival time in patients with metastatic CRC. Nevertheless, drug resistance resulted in poor patient prognosis.

Cancer susceptibility candidate 15. Cancer susceptibility candidate 15 (CASC15) is located at chromosome position 6p22.3 in humans and is expressed abundantly in gastric cancer [101], lung cancer [102], nasopharyngeal cancer [103], and several other cancer types. CASC15 promotes the proliferation and invasion of tumor cells, resulting in poor clinical prognosis. Gao et al. [13] detected CASC15 expression in tumor tissues and para-carcinoma tissues of 48 patients with CRC (among whom 25 were OXA-resistant, whereas 23 were OXA-sensitive), and observed that the levels of CASC15 in tumor tissues were significantly higher than those in the para-carcinoma tissues. Consistent with this, the levels of CASC15 in the tumor tissues of OXA-resistant patients were higher than those in OXA-sensitive patients, and patients with high CASC15 expression presented worse

prognosis compared with those with low CASC15 expression. *In vitro* investigation revealed that the downregulation of CASC15 expression in CRC cells reversed the resistance of HT29/OXA and HCT116/OXA to OXA. In addition, CASC15 was reported to regulate the resistance of CRC cells to OXA via the miR-145/ABCC1 axis, suggesting it as a potential therapeutic target for chemoresistance in CRC.

LINC00152. LINC00152 is located at chromosome position 2p11.2 in humans. It is 828 nucleotides in length and is involved in cell growth, cycle arrest, EMT, and invasion. LINC00152 binds directly to the enhancer of ZESTE homolog 2, thereby inhibiting p15 and p21 and promoting tumor progression [104, 105]. Moreover, LINC00152 promotes tumor growth via the epidermal growth factor receptor (EGFR)-mediated AKT pathway [106]. Abnormal AKT activation frequently leads to chemotherapy resistance [107]. Yue et al. [108] observed that the LINC00152 expression was higher in SW620 and HT29 cells compared to SW480 and Caco-2 cells and that the sensitivity of SW620 and HT29 cells to OXA-induced apoptosis was prominently lower than that of SW480 and Caco-2 cells. LINC00152 overexpression increased the expression of ERBB4 protein in SW620 and HT29 cells, downregulated miR-193a-3p, and decreased the sensitivity of these two cell lines to L-OHP as well as decreased cell apoptosis. Opposite effects were observed upon lowering the LINC00152 expression. In addition, increased sensitivity of cells to OXA-induced apoptosis was observed in colon cancer cells transfected with control or LINC00152 shRNA after blocking the AKT signaling pathway using MK2206 and IGF-1, demonstrating that LINC00152 is involved in the resistance of colorectal cells to L-OHP through regulation of the miR-193a-3p/ERBB4/AKT axis. Huang et al. [109] confirmed that LINC00152 expression was significantly increased in CRC tissues and that LINC00152 promoted the growth and metastasis of CRC cells. Increased LINC00152 expression antagonized 5-FU-induced apoptosis, whereas loss of LINC00152 expression intensified 5-FU-induced apoptosis. Furthermore, a study exploring the underlying mechanism of LINC00152 function revealed that LINC00152 regulated the activity of NOTCH1 via miR-139-5p adsorption to regulate the growth and metastasis of CRC cells as well as the resistance to 5-FU. Therefore, LINC00152 could serve as a potential biomarker for predicting chemotherapy resistance.

Other lncRNAs. *LncRNA MIR100HG.* MIR100HG, located at chromosome position 11q24.1 in humans, is a microRNA host gene [110] having three microRNA sequences in its introns, namely, mir-100, mir-125b-1, and let-7a-2. MIR100HG is either upregulated or downregulated in several human tumor tissues. For instance, MIR100HG expression is suppressed in non-small cell lung cancer compared with normal lung tissue [111]. In contrast, in gastric cancer [112], triple-negative breast cancer [113], and laryngeal squamous cell carcinoma [114], the MIR100HG expression is higher compared with that in normal control tissues and is associated with the clinical prognosis of patients. Fan et al. [110] established cetuximab-resistant CRC cell lines and performed whole-genome sequencing and RNA sequencing. The sequencing results revealed that the transcript with the most upregulated expression in cetuximab-resistant cell lines was that of lncRNA MIR100HG. Polymerase chain reaction results revealed that compared with the control group, the expression of lncRNA MIR100HG, pri-miR-100, and pri-miR-125b-1, as well as their corresponding mature miRNAs (miR-100 and miR-125b), increased in cetuximab-resistant cell lines. In addition, the authors collected 10 pairs of matched tumor tissues from advanced patients with non-KRAS mutations who received treatment with cetuximab before and after the treatment and verified the dysregulation of lncRNA miR100 hg, miR-100, and miR-125b in tumor tissues of these patients. Fluorescence *in-situ* hybridization (FISH) results revealed that signals for MIR100HG, miR-100, and miR-125b in tissues of seven patients (including two patients with secondary NRAS and KRAS mutations) were significantly enhanced in advanced tumors compared to pre-treatment. These findings provide a novel strategy for overcoming cetuximab resistance in clinical cases.

KCNQ1 overlapping transcript 1. KCNQ1 overlapping transcript 1 (KCNQ1OT1) is a common lncRNA that acts as a signal molecule. It is located at chromosome position 11p15.5 in humans. In addition to binding to chromatin, KCNQ1OT1 inhibits the expression of the KCNQ1 gene by recruiting the PRC2 complex and histone methyltransferases specific to H3K9 and H3K27. Zhao et al. [14] reported an abnormally upregulated KCNQ1OT1 expression in CRC tissues and cell lines. Further investigation revealed that KCNQ1OT1 downregulation increased the sensitivity of CRC cells to MTX while decreasing the activity and proliferation capacity of HT29/MTX cells, which promoted tumor cell apoptosis and delayed cell cycle. Studies exploring the mechanism have demonstrated that KCNQ1OT1 is involved in the regulation of CREB and CBP genes and the activation of the cAMP signaling pathway via "sponge adsorption" of miR-760. Several studies on chemotherapy resistance have reported an association between KCNQ1OT1 and drug resistance. KCNQ1OT1 downregulation is reported to significantly inhibit the proliferation and invasion of A549 cells and promote their apoptosis. The KCNQ1OT1 expression is significantly increased in tumor tissues of patients with paclitaxel-resistant lung adenocarcinoma. The KCNQ1OT1 downregulation markedly inhibited chemotherapy resistance of A549/PA cells as well as the expression of its multi-drug resistance 1 (MDR1) protein [115]. Moreover, Zeng et al. [116] reported the regulation of OXA resistance by KCNQ1OT1 in liver cancer cells via the miR-7–5p/ABCC1 axis. For summarization of the roles of all discussed lncRNAs see Table 1 and for summarization of the mechanism axis of all discussed lncRNAs related to chemotherapy resistance see Figure 1.

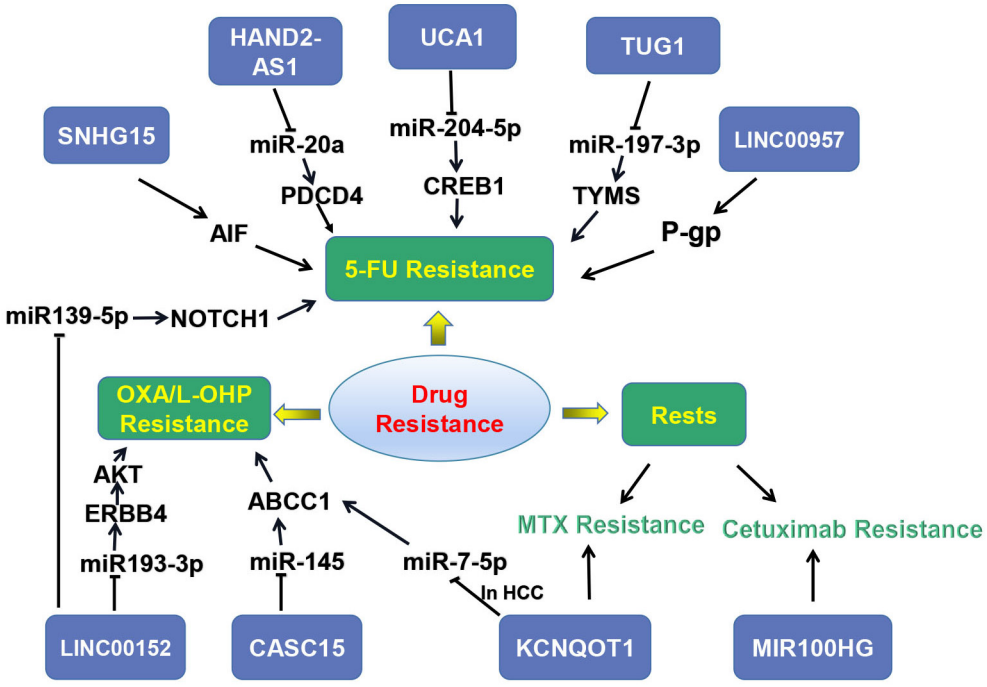

Figure 1. Potential mechanism axis of discussed lncRNAs related to chemotherapy resistance in CRC.

Summary and prospects

With developments in the field of bioinformatics, lncRNAs have attracted considerable attention from several academicians. Numerous lncRNAs have been reported to be involved in the complex regulatory network involved in the development of CRC, playing important roles in the diagnosis, treatment, and prediction of prognosis in CRC. Moreover, recent studies have demonstrated the role of lncRNAs in disease development, metastasis, and drug resistance in CRC. Nonetheless, several challenges are being encountered in this research area. First, low levels of lncRNAs in the body fluids or tissues warrant the use of advanced and reliable methods to amplify and enrich lncRNAs. Second, most of the studies in this area are currently in the initial stage, and the identification of novel tumor biomarkers with better sensitivity and specificity is, therefore, imperative to improve the diagnosis of CRC. Furthermore, determining the actual critical lncRNAs in CRC is a challenge as well, considering the effects of race, subject population, TNM stage, or other confounding factors. Despite these challenges, lncRNAs have immense potential in the early diagnosis, treatment efficacy estimation, and prediction of prognosis in CRC, and are expected to become efficient molecular biomarkers and clinical therapeutic targets for enhanced diagnosis and treatment of CRC.

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