Review Article

The functions of long non-coding RNAs in colorectal cancer

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Abstract: Colorectal cancer (CRC) is the third most prevalent malignant neoplasm worldwide. Recently, in terms of the mechanism of CRC, most studies have focused on protein-coding genes. However, studies have increasingly shown that long non-coding RNAs (lncRNAs) play crucial roles in the proliferation and metastasis of CRC. Investigating this molecular mechanism may provide potential diagnostic tools and therapeutic targets for CRC. This review closely examines the dysregulation of lncRNAs in CRC. On account of different mechanisms being involved in the occurrence and development of CRC, there are several categories of lncRNAs, including lncRNAs related to the Wnt/β-catenin pathway, epithelial mesenchymal transition, epigenetic regulation, angiopoiesis, and chemoresistance. This review summarizes lncRNAs related to the progression of CRC, which may provide insight into the mechanisms and potential markers for prognostic prediction and monitoring relapse of CRC.

Keywords: Long non-coding RNAs (lncRNAs); colorectal cancer (CRC)

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Introduction

Colorectal carcinoma (CRC) is a common digestive tract tumours. At present, new cases of CRC rank third in malignant tumours, after lung cancer and breast cancer, and mortality ranks fourth among malignant tumours after lung cancer, liver cancer and stomach cancer. Tumour progression and metastasis are the primary causes of death, and many patients have advanced stages with metastasis already having occurred at diagnosis due to the atypical symptoms of CRC (1,2). Hence, chemotherapy, radiotherapy and targeted therapy, even immunotherapy, is required in these patients' post-surgery, but outcomes remain unsatisfactory. Due to alterations in multiple genes and epigenetics, tumours regulate initiation and inactivation of oncogenes or tumour suppressor genes, enabling tumour cells to acquire stronger invasion abilities, enter the systemic circulation, evade monitoring of immune cells, and finally colonize distant organs. This complex process is necessary for tumour metastasis (3). Therefore, more investigators are aware of the urgent need to further understand the pathogenesis and corresponding molecular mechanisms of CRC, which will contribute to identification of therapeutic targets and diagnostic biomarkers.

Long non-coding RNAs (lncRNAs) are a type of RNA containing more than 200 nucleotides. Much evidence has shown that lncRNAs have the ability to combine with DNA, RNA and proteins. By binding to DNA promoters, lncRNAs can prevent transcription factors from accessing their own promoter binding sites, impeding the transcription of specific genes to regulate epigenetic silencing of target genes. Many studies have

also reported that lncRNAs can even serve as molecular scaffolds connecting two or more proteins in functional complexes or to position protein complexes at appropriate cellular compartments. In terms of improving mRNA stability, lncRNAs can target antisense mRNA by directly complementing the sequence, thereby regulating selective splicing processes or protecting the 3'UTR from binding by miRNA. In addition, increasing experiments have confirmed that lncRNAs contain binding sites for miRNAs and represent potential molecular sponges for sequestering the most abundant miRNAs. In other words, lncRNAs may act as competing endogenous RNAs for the function of miRNAs, thus protecting miRNA targets (4). In recent years, lncRNAs have been increasingly found to play critical roles in a wide range of biological processes, such as cancer cell proliferation, invasion, apoptosis, metastasis and chemoresistance, including in CRC. Therefore, lncRNAs have been identified as future diagnostic, therapeutic, and/or prognostic cancer biomarker (5-7). The objective of this review was to summarize lncRNAs related to the Wnt/β-catenin pathway, epithelial mesenchymal transition, epigenetic regulation, angiopoiesis, and chemoresistance.

LncRNAs related to the Wnt/β-catenin pathway

Wnt/β-catenin signalling is critical for CRC initiation (8). Casein kinase 1 (CK1), glycogen synthase kinase 3β (GSK-3β), Axin, protein phosphatase 2A (PP2A), and APC and activator protein 2α (AP-2α) are all significant in the Wnt signalling pathway (9). Dysfunction of these factors leads to activation of Wnt signalling by converting free β-catenin accumulated in the nucleus and then stimulating the E2F transcription factor-4 (E2F4), the proto-oncogene c-Myc, and cyclin D1 (CCND1), which are targets of the lymphoid enhancing factor (LEF)/T-cell factor (TCF) (10).

The lncRNA colorectal neoplasia differentially expressed (CRNDE), which is transcribed from chromosome 16 on the strand opposite the adjacent *IRX5* gene, is a novel biomarker in CRC and other solid cancers. CRNDE has been shown to be elevated in CRC cells and promotes the proliferation of CRC cells via miR-181a-5p-mediated regulation of Wnt/β-catenin signalling. Han *et al*. (11) reported that β-catenin and TCF4 are inhibitory targets of miR-181a-5p, and Wnt/β-catenin signalling is activated by both CRNDE overexpression and miR-181a-5p knockdown. Finally, they indicated that CRNDE may represent a prominent therapeutic target in CRC.

Zhang *et al*. (12) reported that cancer susceptibility candidate 11 (CASC11) is upregulated in CRC tissues, further demonstrating that c-Myc directly binds to the promoter regions of CASC11 and enhances CASC11 expression by increasing promoter histone acetylation, and finally, CASC11 aligns with heterogeneous ribonucleoprotein K (hnRNP-K) to activate Wnt/β-catenin signalling in CRC cells. Increasing expression of CASC11 conclusively leads to proliferation and metastasis of CRC.

Another oncogene, the lncRNASLCO4A1-AS1, which has been confirmed to have high expression in various cancers, especially in CRC, activates Wnt signalling to initiate tumorigenesis. Yu *et al*. (13) discovered that expression of the lncRNASLCO4A1-AS1 is significantly upregulated in CRC tissue and cell lines, which activates Wnt/β-catenin signalling via enhancing the stability of β-catenin. Finally, accumulation of β-catenin protein in the nucleus enhances proliferation, migration and invasion in SLCO4A1-AS1-depleted CRC cells, suggesting that SLCO4A1-AS1 may represent a novel therapeutic target.

The lncRNA NEAT1 (nuclear paraspeckle assembly transcript 1), which is located at 11q13.1, is upregulated in CRC cells. NEAT1 was identified as a novel regulator of the Wnt/β-catenin pathway in CRC. Many studies have uncovered that NEAT1 may act as a competing endogenous RNA (ceRNA) via sequestering miRNAs (14). In Yang Luo's research, they deduced that NEAT1 was abnormally highly expressed and significantly activated the Wnt/β-catenin signalling pathway. It primarily functions as a ceRNA for miR-34 to repress SIRT1 expression. Taken together, their findings demonstrate that the lncRNA NEAT1 may represent a prognostic biomarker and a potential therapeutic target in CRC (15).

In contrast, many other lncRNAs, such as LINC00675, CTD903, SNHG1, TINCR and BC0209135 (16-20), were recently proven to be tumour suppressors in CRC. High levels of these factors were suggested to inhibit Wnt/β-catenin signalling in CRC (*Figure 1*).

LncRNAs affect epithelial mesenchymal transition (EMT)

EMT is an important way to promote tumour cell metastasis. Its pathological features include epithelial cells losing their polarity and losing adhesion to other cells, while gaining the ability to migrate and infiltrate, making quiescent epithelial cells transform into motile mesenchymal cells (21,22). Characteristic changes of EMT

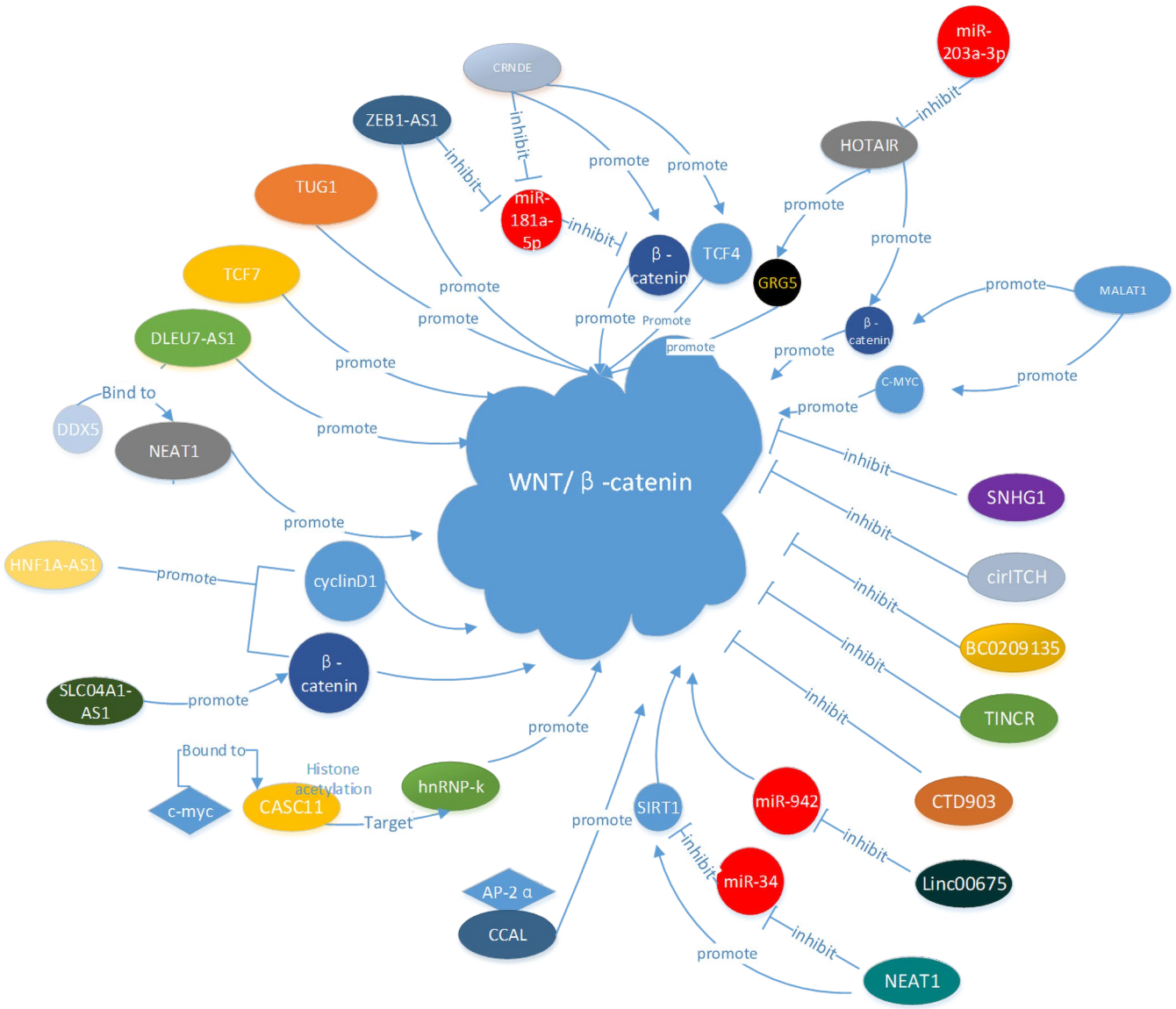

Figure 1 LncRNAs affect Wnt/β catenin pathway in CRC cells. c-Myc bound to CASC11 and increased promoter histone acetylation to enhance CASC11 expression, then CASC11 target heterogeneous ribonucleoprotein K (hnRNP-K) to activate Wnt/β-catenin signaling pathway; CCAL targeted activator protein 2α (AP-2α), and activated Wnt/β-catenin pathway; NEAT1 promoted Wnt/β-catenin signaling pathway by sponging miR-34 to enhance SIRT1 expression; another study showed that DDX5 bound to NEAT1 to promote Wnt/β-catenin signaling pathway; Linc00675 suppresses miR-942 to promote the Wnt/β-catenin signaling; HNF1A-AS1 stimulated Wnt/β-catenin signaling pathway activity by upregulating the expression of β-catenin,cyclinD1; ZEB1-AS1 inhibits miR-181a-5p and provokes ZEB1 to promote Wnt/β-catenin signaling pathway; CRNDE inhibited miR-181a-5p and provokes β-catenin and TCF4 to promote Wnt/β-catenin signaling pathway; MALAT1nduced Wnt/β-catenin signaling pathway by promoting c-Myc and β-catenin; CTD903, TINCR, BC0209135, cirTCH, SNHG1 inhibited Wnt/β-catenin signaling; DLEU7-AS1, TCF7, TUG1 promoted Wnt/β-catenin signaling; miR-203a-3p downregulated HOTAIR, which increasing β-catenin and GRG5 to facilitate the Wnt/β-catenin signaling. LncRNAs, long non-coding RNAs.

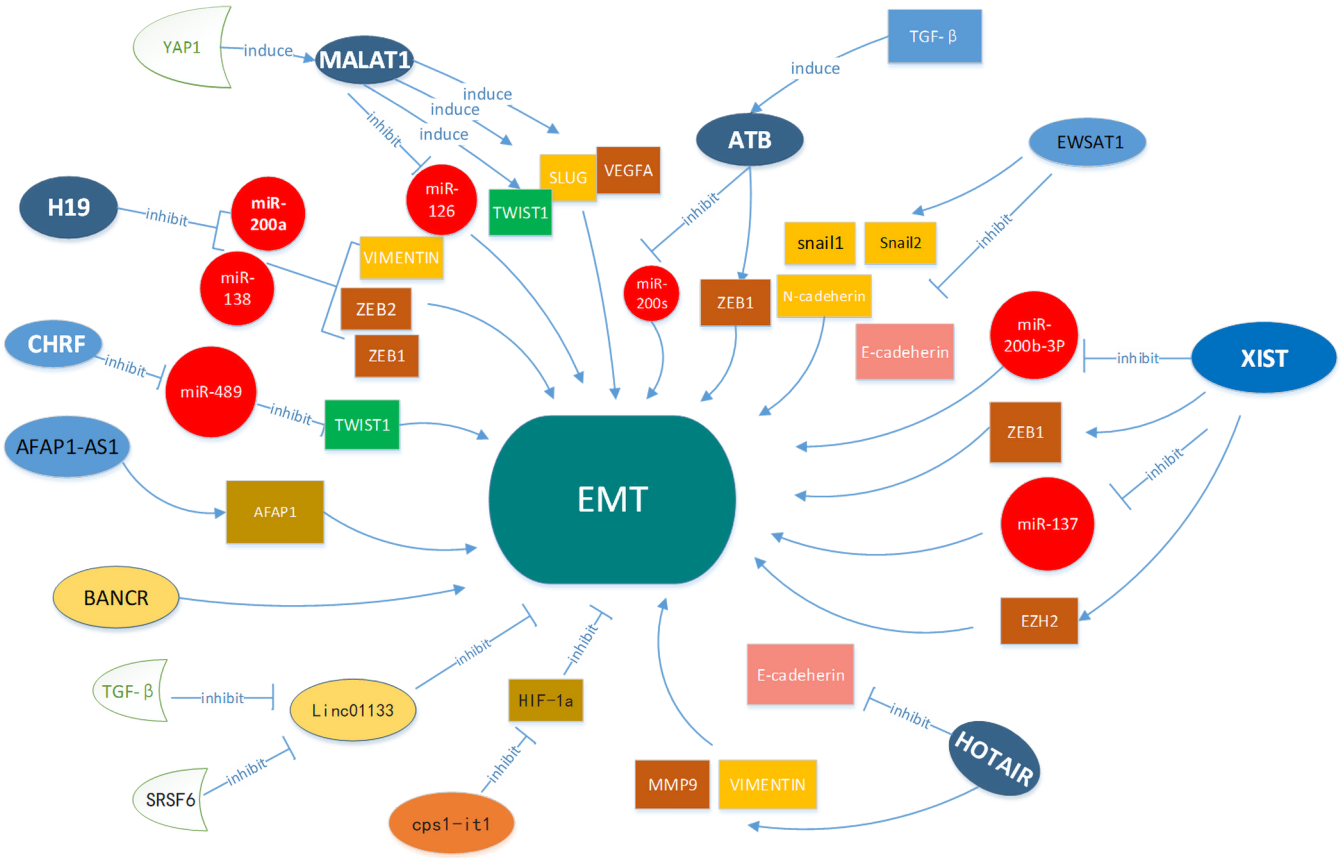

Figure 2 LncRNAs affect epithelial-mesenchymal transition in CRC cells CHRF inhibits the expression of miR-489 and provokes TWIST1 to promote EMT; H19 inhibits miR-138 and miR-200a then induces Vimentin, ZEB1, and ZEB2 to promote EMT; YAP1 induces lncMALAT1, which inhibits miR-126-5p and provokes ZEB1 to promote EMT; TGF-β induces lncATB, which inhibits miR-200s and provokes ZEB1 to facilitate EMT; EWSAT1promotes EMT by increasing snail1, snail1 and N-cadherin, and decreasing E-cadherin. XIST bind with miR-200b-3p, and increase the expression of the ZEB1 to promote EMT, at the same time, XIST bind with miR-137, and increase the expression of the EZH2 to promote EMT; HOTAIR promoted the EMT by decreasing E-cadherin and increasing vimentin and MMP9; AFAP1-AS1 encoding AFAP1 stimulate EMT; BANCR was upregulated and promoted EMT; TGF-β downregulate Linc01133 and inhibit EMT; cps1-it1reversed the EMT by inhibiting HIF-1a. LncRNAs, long non-coding RNAs; CRC, colorectal cancer.

include downregulation of E-cadherin and upregulation of N-cadherin, ZEB1, ZEB2, snail1 and snail2. Accumulating evidence has confirmed that EMT plays a vital role in CRC metastasis, and many lncRNAs induce CRC metastasis via EMT (*Figure 2*). These factors can be divided into two categories, one of which is upregulated in CRC and is defined as oncogene, while another classic lncRNA is downregulated and is defined as a tumour suppressor gene, affecting EMT and inducing metastasis.

As the first imprinted gene to be discovered, the lncRNA H19 gene is mapped to chromosome 11 in humans and was defined as a maternally expressed imprinted gene that plays an important role in mammalian development (23). Ding *et al.* (24) reported that lncRNA H19 is upregulated in CRC compared to adjacent normal colorectal mucosa cells and that expression of E-cadherin is increased, while expression of vimentin and snail is decreased. Liang *et al.* (25) found that H19 expression was significantly increased in mesenchymal-like cancer cells and CRC tissues, significantly stimulating EMT progression and inducing tumour growth both *in vivo* and *in vitro*. Furthermore, they confirmed that H19 adsorbs miR-138 and miR-200a by sponge-like adsorption, inhibiting their function and resulting in unrestricted production of their endogenous targets,

Vimentin, ZEB1 and ZEB2, which are core marker genes of mesenchymal cells. Taken together, these experimental phenomena suggest that lncRNA H19 regulates expression of multiple EMT-related genes by acting as a competitive endogenous RNA, potentially constituting a link between regulation of miRNA networks and EMT progression. In addition, Liang *et al*. (26) found that the sTLR4/MD-2 complex inhibits CRC migration and invasion by lncRNA H19 downregulation both *in vitro* and *in vivo*.

LncRNA EWSAT1 (Ewing sarcoma-associated transcript 1), which is located at chromosome 15, has been confirmed to be highly expressed in various tumour tissues, promoting the occurrence and development of cancers, including CRC. EWSAT1 is overexpressed in CRC tissues compared to matched adjacent normal tissues, and higher expression of EWSAT1 promotes EMT by reducing E-cadherin expression and increasing snail1, snail2 and N-cadherin expression. Therefore, EWSAT1 was deduced to be an oncogene that promotes metastasis via initiation of EMT progression (27).

MALAT1 (metastasis associated lung adenocarcinoma transcript 1), a transcriptional regulator for numerous genes, including genes involved in cancer metastasis and invasion, is primarily localized in the cytoplasm of colon cancer cells according to cell fractionation assays. The lncRNA MALAT-1 is reportedly upregulated by YAP1 in CRC tissues, stimulating expression of metastasis-associated molecules, such as TWIST, SLUG, and VEGFA, by sponging miR-126-5p in CRC to affect EMT (28).

LncRNA-ATB is located on human chromosome 14:19,858,667–19,941,024. lncRNA-ATB has been indicated to be a transcript with two exons spanning more than 80 kb. lncRNA-ATB is upregulated in response to overexpression of transforming growth factor-β (TGF-β), and many studies have shown that lncRNA-ATB induces EMT, leading to the promotion of tumour progression, i.e., enhancement of proliferation, migration, and invasion (29). Yue *et al*. (30) demonstrated that expression of lncRNA ATB is significantly upregulated in CRC tissue and cell lines compared to adjacent normal mucosa; however, E-cadherin was decreased in cancer tissues. Reduced levels of E-cadherin result in decreased adhesion strength between cells in a tissue, leading to increased cellular activity and facilitating cancer cell invasion to surrounding tissues through the basement membrane and into systemic circulation. Further studies (31) showed that lncRNA ATB induces ZEB1 expression by inhibiting miR-200s in tumour cells to affect EMT in colorectal neoplasm cells.

Many studies have reported that lncRNA X-inactive specific transcript (lncRNA XIST) is highly expressed in multiple tumours. Chen *et al*. (32) reported that expression of lncRNA XIST is upregulated in both CRC cell lines and tissues. High expression of lncRNA XIST promotes CRC cell proliferation and invasion through EMT progression, and further study confirmed that lncRNA XIST directly binds to miR-200b-3p, increasing expression of ZEB1, a direct target of miR-200b-3p. Liu *et al*. (33) reported that lncRNA XIST promotes EMT progression by regulating the miR-137-EZH2 axis.

Another lncRNA, HOTAIR (HOX transcript antisense RNA), which is located on chromosome 12q13.13, has been considered a proto-oncogene in a variety of tumours and was found to demonstrate trans-transcriptional regulatory function. To further investigate its biological functions, studies have shown that lncRNA HOTAIR is elevated in CRC tissues and promotes EMT progression by increasing expression of vimentin and matrix metallopeptidase9and decreasing expression of E-cadherin. Therefore, HOTAIR may serve as a very promising predictor and therapeutic target for CRC (34).

As a well-known lncRNA, actin filament associated protein 1 antisense RNA1 (AFAP1-AS1) is an antisense RNA gene encoding AFAP1, which is also highly expressed in CRC. Western blot results showed that expression of E-cadherin was elevated, however, expression of N-cadherin, vimentin, and fibronectin was reduced when AFAP1-AS1 was knocked-down, confirming that AFAP1-AS1 participates in cell proliferation, colony formation, migration and invasion via the EMT pathway (35).

The BRAF-activated non-coding RNA (BANCR) is a lncRNA with a length of 693 bp located on chromosome 9, and numerous studies have shown that BANCR is involved in many biological processes, including EMT progression. It has been proven that BANCR is upregulated in CRC and induces EMT via a mitogen-activated protein kinase kinase/extracellular signal-regulated kinase-dependent mechanism, enhancing G0/G1 cell cycle arrest and apoptosis by regulating p21. These findings indicate that BANCR plays an important role in CRC and may represent a novel and useful biomarker (6,36).

The lncRNAs expounded above are all upregulated as oncogenes that promote EMT; however, there are many lncRNAs that are downregulated in CRC and are defined as tumour suppressor genes that inhibit EMT progression.

LINC01133, another novel lncRNA with reduced expression in CRC, was shown by Kong *et al*. (37) to be

downregulated by TGF-β, which inhibited EMT and metastasis in CRC cells. Furthermore, they found that EMT was affected by LINC01133 in CRC cells and was dependent on the existence of SRSF6. As a target mimic, Linc01133 was defined as a prognostic biomarker and an effective target for anti-metastatic therapies for CRC.

LncRNA CPS1 intronic transcript 1 (lncRNA CPS1-IT1), was recently identified as a tumour suppressor, and Zhang *et al*. (38) found that lncRNACPS1-IT1is significantly decreased in CRC, resulting in worse prognosis. As a tumour suppressor, CPS1 reverses EMT of tumours by inhibiting hypoxia-induced autophagy through inactivation of HIF-1α in CRC. These findings suggest that lncRNA CPS1-IT1 affects EMT progression and inhibits tumour invasion and metastasis.

Epigenetic regulation in CRC

Recent genomic analyses have uncovered epigenetic regulation as a major driver of tumorigenesis (39), lncRNAs can be cytoplasmic and/or nuclear, and nuclear lncRNAs reportedly regulate histone and DNA modifications (40). Therefore, at both the histone and DNA methylation levels, many lncRNAs have been found to bind to epigenetic complexes and play roles in controlling the DNA modification system in CRC cells (41-44) (*Figure 3*).

The nucleoli and paraspeckles maintain a unique morphology in the nucleus and play vital roles in transcriptional activity. NEAT1 and MALAT1, which are overexpressed in CRC tissues, have been shown to play a significant role in the formation and organization of nuclear speckle bodies, leading to poor disease prognosis (45,46). Another lncRNAs, such as NEAT1 and LUCAT1, interfere with miRNA and DNMT, affecting DNA methylation (47,48).

LncRNAs also may interact with multicomb inhibitory complex 2 (PRC 2), in which the three main subunits are embryonic ectoderm development (EED), SUZ12, and ZEST homology enhancer (EZH2) in embryonic ectoderm development. Approximately 20–30% of lncRNA genes have been confirmed by RNA immunoprecipitation to interact with PRC2 by binding to SUZ12 and EZH2 (49). In CRC cells, there are many lncRNAs, such as AFAP1-AS1 (50), ANCR (51), BLACAT (52), CRNDE (53), HOTAIR (54), HULC (55), PINT (56), SNHG17 (57), UCA1 (58-60), that bind to EZH2. LncRNAs solicit PRC2 from gene promoters/enhancers, which are genetically silenced by trimethyl lysine 27 (K27me3) stimulation of histone H3 (H3K27me3). In addition to the lncRNA/EZH2 combination, there are some lncRNAs, such as HOTTIP (61), CASC15 (62), GClnc1 (63), and HOXD-AS (64), that interact with the adaptor protein WDR5 from the histone H3 lysine4 (H3K4) methyl transferase complex. In contrast, HOTTAIR (65), FOXP4-AS1 (66), HOXA11-AS (67), and HOXA-AS2 (68) interact with histone lysine-specific demethylase 1 (LSD1), which may also affect histone demethylation.

LncRNAs interact with switching defective sucrose/non-fermenting (SWI/SNF) complexes, affecting chromatin configuration and DNA methylation. SWI/SNF complexes have three subunits, Brahma related gene 1 (BRG1), SNF5 and BAF200a. It has been shown that lncTCF7 (69), lncFDZ6 (70), NEAT1 (71), and UCA1 (72) bind to BRG1 and SChLAP1 (73), while MVIH (74) binds to SNF5 and BAF200a.

Antisense coding lncRNAs, such as HAGLR, GAS5, NEAT1, H19, PINT, and CRNDE, which were reportedly associated with chromatin looping, directly suppress the transcription of sense coding genes, and their overexpression leads to poor prognosis in CRC (75).

Recently, many studies have confirmed specific functions of a number of p53-regulated lncRNAs, including LincRNA-p21, PURPL, PANDA, NEAT1, DINO, PINT, LED, PR-lncRNA-1, Linc-475 and PINCR. Li *et al*. (76) investigated PURPL, the lncRNA that is regulated by p53, which inhibits basal p53 levels and facilitates tumorigenicity in CRC via associating with MYBBP1A and inhibiting formation of the p53-MYBBP1A complex.

Another lncRNA, colon cancer-associated transcript 2 (CCAT2), is an RNA with the length of 1,752 bp located on chromosome 8q24.21. This genomic locus harbors the SNP rs6983267 (77), which plays a vital role in colorectal cancer. It has been revealed that lncRNA CCAT2 expression levels remarkedly elevated in CRC tissues compared to paired normal mucosae. In Ling *et al*.'s experiment (78), they confirmed that high expression of CCAT2 is one of the primary characteristics of microsatellite-stable (MSS) CRCs that leads to chromosomal instability (CIN), and the centrosome defects they observed may lead to abnormal chromosome breakage and fusion, eventually leading to aneuploidy. Further studies found that overexpression of CCAT2 leads to higher expression of the *MYC* gene, as well as expression of downstream MYC protein-coding gene targets, such as BAX, CDC25A and CDKN2A, as well as microRNA targets, such as MIR17HG.Taken together, CCAT2 is a useful diagnostic indicator and therapeutic

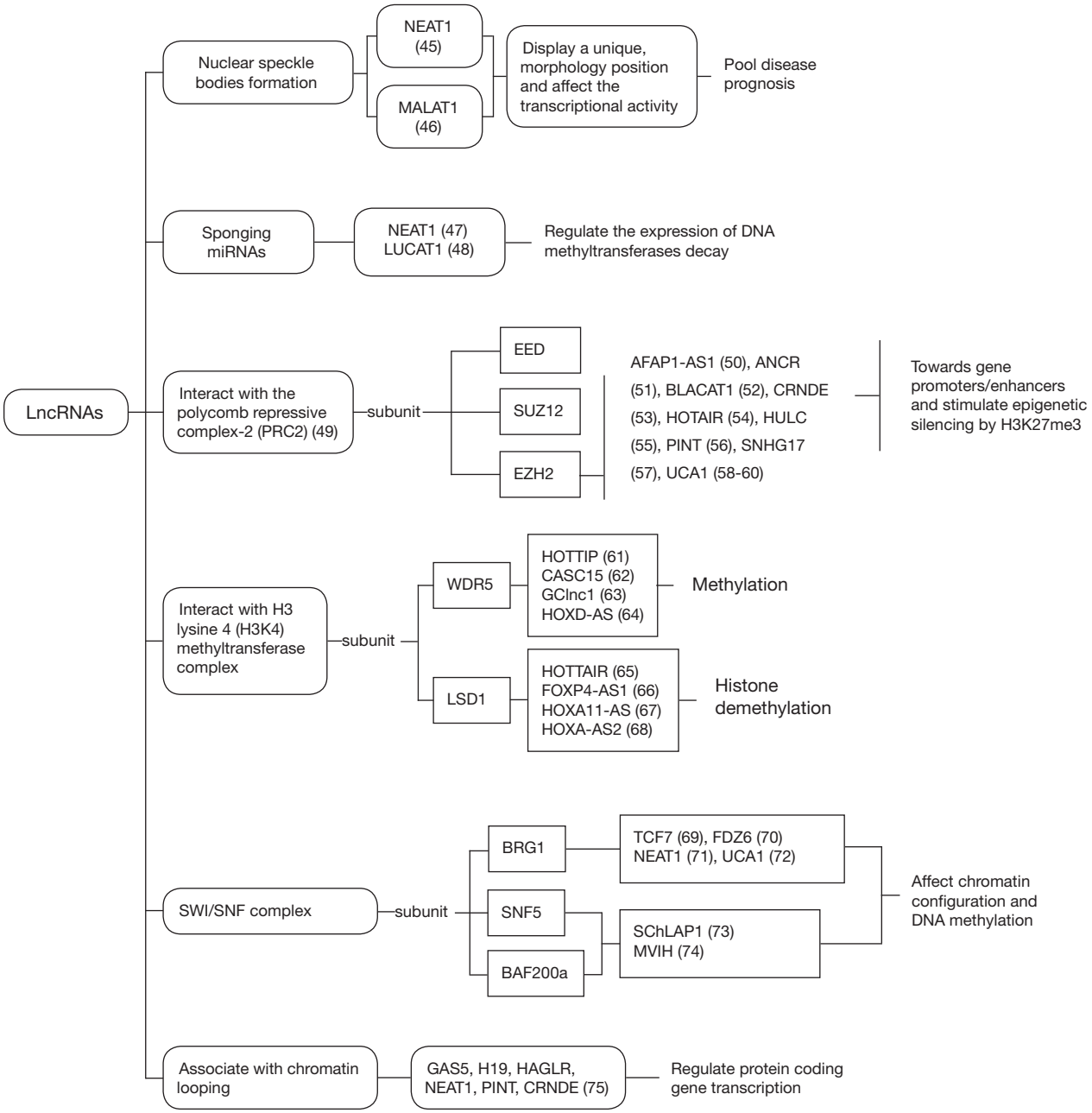

Figure 3 Epigenetic regulation in CRC. CRC, colorectal cancer.

target.

Accumulating evidence has shown that expression levels of lncRNAs are positively correlated with patient prognosis in CRC, indicating that lncRNAs play a critical role in modulating the cancer epigenome and may be significant targets for CRC diagnosis and therapy.

LncRNAs and angiogenesis

Ample evidence indicates that tumour growth and metastasis are accompanied by the formation of tumour blood vessels. Growth of tumour blood vessels not only provides nutrition for tumours but also provides a pathway for metastasis (79). There is increasing evidence that lncRNAs play a vital

role in tumour angiogenesis (80). However, in CRC, there are no studies examining the effect of lncRNA on angiogenesis. Using enzyme-linked immunosorbent assay (ELISA) and RNA pull-down (RIP) methods, lncRNA MVIH was shown to attenuate angiogenesis via inhibiting the secretion of PGK1 (phosphoglycerate kinase 1), a key factor for angiogenesis (81). The lncRNA MALAT1 has also been shown to cause tumour angiogenesis. MALAT1 activates angiogenesis by regulating vascular density and vasodilation (82,83), while MEG3 is reported to reduce the formation of tumour blood vessels by affecting expression of VEGF (84). Recently, H19, LincRNA-p21, TUG1 and HOTAIR have all been confirmed to play important roles in tumour angiogenesis. Interestingly, these lncRNAs have also been shown to play important roles in the development of CRC. Therefore, these lncRNAs are likely to be involved in the formation of blood vessels in colorectal tumours, which is a hot topic for further research.

Chemoresistance

Chemotherapy resistance is an important reason for the failure of advanced CRC treatment. In recent years, many studies have shown that lncRNAs play an important role in tumour chemotherapy resistance. Li *et al*. (85) confirmed that lncMEG3 is downregulated in oxaliplatin-resistant CRC patients and has considerable potential for identification of responsive and non-responsive patients. In addition, in patients with CRC treated with oxaliplatin, those with reduced serum MEG3 expression experience increased chemoresistance and reduced survival. They demonstrated that expression of lncRNA MEG3 is reduced in CRC, with consequent poor response to therapy. The main mechanism for this effect involves lncRNA MEG3 increasing chemosensitivity by enhancing oxaliplatin-induced apoptosis. Therefore, overexpression of MEG3 may be a novel therapeutic direction for CRC patients to reverse oxaliplatin resistance.

Another lncRNA, UCA1, weakens the response to 5-fluorouracil (5-FU) chemosensitivity in CRC by reducing apoptosis via inhibiting miR-204-5p. The UCA1-miR-204-5p-CREB1/BCL2/RAB22A regulatory network plays a vital role in pathogenesis and chemoresistance in CRC patients (86). In addition, Wu *et al*. (87) posited that UCA1 sequesters miR-204 by regulating HMGA2 in CRC cells, affecting chemoresistance. Lee *et al*. (88) showed that upregulation of the lncRNA snaR increases cell death after treatment with 5-FU, which manifests as snaR loss increasing resistance to 5-FU in CRC. Linc00152 sequesters miR-193a-3p and elevates levels of ERBB4, which contribute to oxaliplatin chemosensitivity in colon cancer (89). Li *et al*. verified that lncRNA TUG1 is significantly increased in CRC, causing methotrexate resistance. They also found that lncRNA TUG1 sequesters miR-186, and cytoplasmic polyadenylation element binding protein 2 (CPEB2) is negatively correlated with expression levels of miR-186. As such, they propose that lncRNA TUG1 mediates MTX resistance in CRC via the miR-186/CPEB2 axis. As previously mentioned, the lncRNA CCAL induces CRC cell multidrug-resistance through activation of Wnt/β-catenin signalling by inhibiting AP-2α and leading to upregulation of MDR1/P-gp expression (90). AP-2α serves as an oncosuppressive protein by interacting with APC and β-catenin.

Conclusions

Accumulating evidence has proven that lncRNAs play significant roles in tumorigenesis and development of CRC. In this review, we summarized abnormal expression of lncRNAs that heavily influence different biological progresses, including the Wnt/β-catenin signalling pathway, EMT, angiogenesis, epigenetic regulation and chemoresistance. In CRC diagnosis, due to their convenience and non-invasiveness, biomarkers in plasma and serum perform a vital function for comparing colonoscopy examinations. However, in the current blood test, the best biomarkers, carcinoembryonic antigen (CEA) and carbohydrate antigen19-9 (CA19-9), exhibit low specificity and sensitivity, particularly in early stage CRC. Therefore, the main priority is identifying novel biomarkers to reliably detect early CRC and relapse in patients' post-surgery. First, lncRNAs are regarded as targets of tumour prediction. Abnormal expression of lncRNAs affects tumour development. Intriguingly, recent studies have shown that some lncRNAs can be detected in the serum of cancer patients. For instance, detection of lncRNA CRNDE-h in exosomes shed light on utilizing exosomal CRNDE-h as a non-invasive serum-based tumour marker for diagnosis and prognosis of CRC (91). Several other dysregulated lncRNAs, such as BANCR, NR_029373, NR_026817, and NR_034119, are present in both cancer tissues and patient serum samples (92). There is concern that a single lncRNA may not be sufficient for predicting CRC prognosis. However, if several lncRNA combinations that were known to be involved in CRC progression were identified, it might

solve the issue. It is also worth considering whether there are different sub-classifications of lncRNA expression in patients with cancer at different sites in CRC. Barbagallo *et al.* recently found that TUG1, a tumour suppressor gene, is decreased in CRC tissues but increased in exosomes, while UCA1, which acts as an oncogene, displays the opposite behaviour. This observation suggests that tumour cells secrete lncRNAs through exosomes to protect themselves from TUG1 tumour-suppressive activity. The oncogenic function of UCA1 is critical to tumour progression, inducing tumour cell proliferation by limiting secretion of UCA1.It is well known that use of a signature of multiple biomarkers is preferable, as it would increase diagnostic and prognostic accuracy of a single test. Barbagallo *et al.* calculated a combination ROC curve considering two lncRNAs with opposite trends in expression that may increase the sensitivity and specificity compared to a single biomarker (93,94). As found in gene mutations before, such as NRAS, BRAS and KRAS genes that well known to be vital in the advancement and development of CRC, increasing lncRNAs are being discovered, and they have been shown to have distinct functions in tumorigenesis and development, such as influencing epigenetics, gene transcription, chemical resistance and so on, including in CRC research. In conclusion, lncRNAs play crucial roles as predictors of cancer. Additional studies with large cohort of CRC patients should be performed in the future to expand these findings.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.08.23). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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