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Review Article

Advances in lncRNA research and colorectal cancer

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Abstract: Colorectal cancer (CRC) is a common digestive tract tumor with an unidentified etiology. Long non-coding RNA (lncRNA) is a kind of RNA with more than 200 nucleotides and no protein-coding functions. It is confirmed that lncRNAs, such as MEG3, HOTAIR, H19, and UCA1, play a role in chemoresistance and distant invasion by regulating the cell cycle and miRNAs and promoting the proliferation of tumor cells in CRC patients. LncRNAs are also valuable in the diagnosis, treatment and prognosis of CRC patients. This article gives an overview of the advances in lncRNA research in CRC.

Keywords: Colorectal cancer, lncRNA, diagnosis, prognosis

Overview of the epidemiology and treatment of colorectal cancer

Colorectal tumors are common digestive tract tumors [1, 2], and have the third and the second highest incidences of tumors in males and females, respectively [3]. Colorectal cancer (CRC) occurs mainly in elderly patients. The incidence of CRC in males is higher than it is in females, and the incidence of colon cancer is higher than it is in rectal cancer [4]. The incidence of CRC is significantly lower in developed countries than in developing countries due to their sound screening means and effective management of early lesions [5]. The incidence of CRC in China is increasing yearly and may be associated with the aging of the population, changes in diet, and the sedentary lifestyle [6-10]. Previous studies have deepened the understanding of CRC, but the pathogenesis is still unclear [11, 12]. Therefore, a better overall understanding of CRC is important for improving its clinical diagnosis and treatment. At present, surgery remains the first choice for the treatment of CRC. For patients who have missed the opportunity for surgery, chemoradiotherapy is also of great significance in improving the quality of life and extending life [13].

The production of lncRNAs

LncRNA, once called as the "metabolite" produced during gene transcription, is transcribed by RNA polymerase II [14]. At present, there are five ways to produce lncRNAs: first, structural alterations of coding genes; second, morphological alterations of genetic materials; third, translocation of non-coding genes during reverse transcription; fourth, tandems of noncoding genes during duplication; fifth, insertions of transposons [15]. Studies have shown the abnormal expression of lncRNA in the tissues of CRC patients indicate that lncRNA is involved in the development of CRC [16, 17]. LncRNA can be expressed differentially in the peripheral body fluids, which makes it a potential indicator for early screening, diagnosis, monitoring, and treatment. This article summarizes the roles of each lncRNA in the diagnosis and treatment of CRC by selecting typical lncRNAs from the aspects of diagnosis, mechanism, and treatment. See **Figure 1**.

The mechanisms of lncRNA in the development of CRC

LncRNA is involved in the development of CRC mainly by binding specific miRNA, then regulating the corresponding mRNA to control the expression of proteins. There are also antineoplastic lncRNAs. For example, a low expression of lncRNA-MEG3, which inhibits the proliferation of cancer cells mainly by controlling cell apoptosis, is found in CRC tissues. RNA-LINC00339 can regulate the expression of

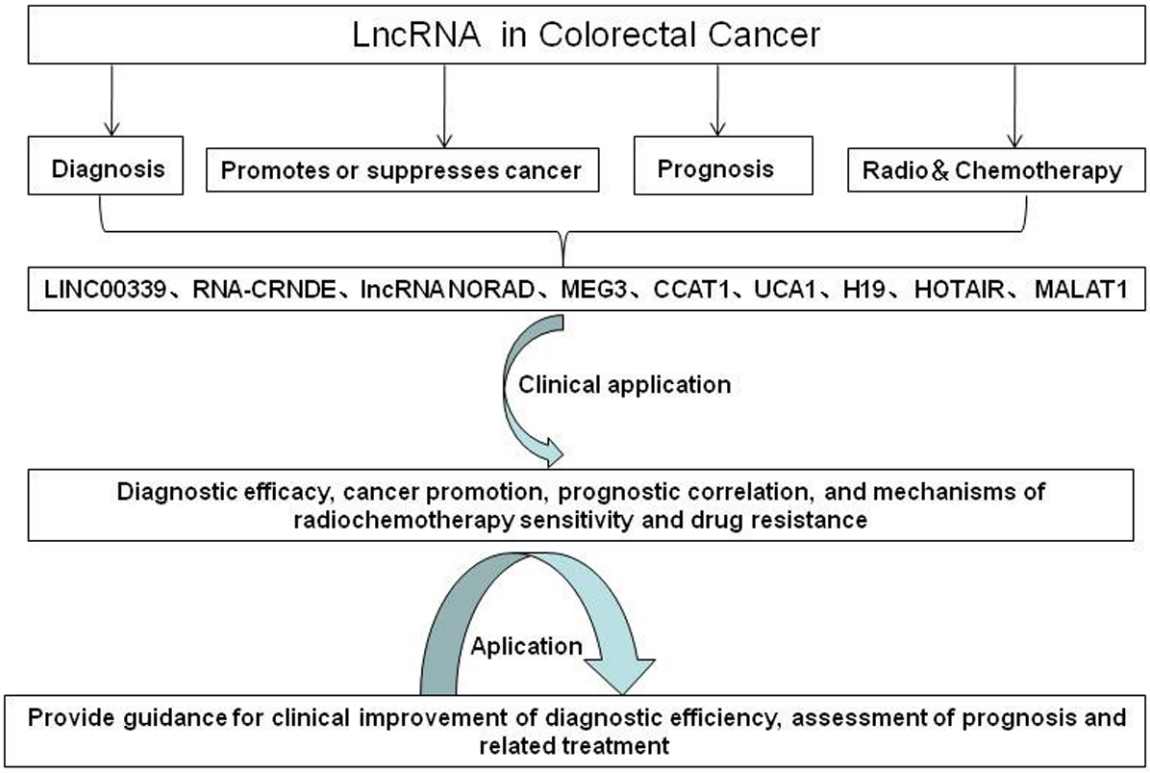

Figure 1. Effects, classic representations. and clinical applications of lncRNA in the diagnosis and treatment of colorectal cancer.

miR218, which inhibits the cell cycle progression, migration, and invasion and promotes the apoptosis of tumor cells in vivo. H19 regulates the expression of the downstream signaling pathway by binding with miR675 [18, 19]. Although the research on lncRNAs in CRC is still at a preliminary stage, it has been confirmed that lncRNAs play a role in the metastasis, diagnosis, treatment, and drug resistance of CRC, which makes lncRNA a first-line target in the diagnosis and treatment of CRC.

Colorectal neoplasia differentially expressed (CRNDE)

It is confirmed that the gene CRNDE is highly expressed in CRC tissues and is positively correlated with patients' clinical TNM staging. A higher expression of CRNDE indicates a poorer prognosis of CRC [20, 21]. The invasive capacity of DLD-1 in cancer cells decrease significantly after the knockdown of CRNDE and increases significantly with a high expression of CRNDE, which confirms that CRNDE exerts its function of promoting the metastasis of CRC cells in vivo [22]. Another study has further confirmed that CRNDE may promote the distant metastasis of CRC cells by activating signal transducer and activator of transcription 3 (STAT3) and accelerating the epithelial-mesenchymal transition (EMT) [23].

Noncoding RNA activated by DNA damage (NORAD)

Studies have confirmed a high expression of lncRNA NORAD in CRC tissues and its expression level are correlated with histological differentiation, lymph node metastasis, and distant organ invasion [24, 25]. lncRNA NORAD plays a role in promoting cancer metastasis by regulating cell proliferation, differentiation and carcinogenesis through E-Twenty-Six-1 (ETS-1). The overexpression of lncRNA NORAD may lead to tumorigenesis, invasion, and metastasis [26, 27]. Moreover, ETS-1 promotes the production of matrix metalloproteinase (MMP), thus promoting matrix protein proteolysis and the angiogenesis of neovascularization, which are the main pathological changes in the distant invasion and metastasis of tumors [28]. This suggests that lncRNA NORAD promotes the distant

metastasis of cancers by controlling ETS-1 and its downstream invasion-related proteins. LncRNA NORAD might prove to be an intervention target for the treatment of advanced cancers [29].

Colon cancer associated transcript 1 (CCAT1)

A high expression of CCAT1, which can promote the proliferation, invasion, and metastasis of CRC cells mainly by up-regulating the expression of E-box elements in the promoter region of CCAT1 through the c-Myc gene, was also found in the CRC tissues [30, 31]. In addition, CCAT 1 can be highly expressed in the peripheral blood, which makes it a recognized diagnostic marker and intervention target [32, 33].

HOX transcript antisense RNA (HOTAIR)

At present, HOTAIR is mainly used as a marker for the diagnosis and prognosis of CRC. Furthermore, the resistance of HOTAIR to chemotherapy has also been found clinically. The biological effects of HOTAIR on promoting cancers and its resistance to chemotherapy are mainly achieved through the miR-203a-3p and Wnt/β-catenin signaling pathways [34, 35]. The latest studies have also shown that a high expression of HOTAIR in the peripheral blood of CRC patients is positively correlated with tumor differentiation, depth of invasion, and TNM staging. Thus, HOTAIR can serve as an important indicator for the early diagnosis and prognosis evaluation of CRC [36, 37]. See **Table 1**.

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1)

MALAT1, located in the 11q13 chromosome, is involved in the development of CRC and the drug resistance to oxaliplatin [38, 39]. MALT1 not only can accelerates the cell cycle and inhibits the apoptosis in tumor cells, it can also regulate EMT by inhibiting the function of miR218 during chemotherapy [40, 41]. Cell experiments have confirm the abnormal expression of MALAT1 in the oxaliplatin-resistant cell line [42]. These results suggest that MALAT1 can be used as a potential target for the treatment and drug resistance of CRC. See **Table 2**.

H19 (Imprinted maternally expressed transcript (non-protein coding))

H19 plays a role in the diagnosis and prognosis of tumors as the precursor of miR-675. The mechanisms mainly include four aspects: first, H19 regulates the expression of miR-675 to inhibit the expression of the suppressor gene for retinoblastoma (RB); second, the absorption and antagonistic effects on miR-138 and miR-200a lead to their consumption or loss of function, which results in the metastasis of tumor cells; third, it promotes the rapid proliferation of cancer cells by regulating the cell cycle; fourth, it is involved in the development of tumors using a bidirectional regulation with the vitamin D receptor (VDR) [43-46]. See **Table 3**.

Maternally expressed gene 3 (MEG3)

Histopathology experiments show that MEG3 is lowly expressed in CRC patients' tissues and is negatively correlated with tumor invasion, lymph node metastasis, and the degree of differentiation. Therefore, MEG3 has a good diagnostic and prognostic value for CRC [47, 48]. The current consensus is that MEG3 exerts an antineoplastic effect and improves the prognosis of patients by promoting the apoptosis of CRC cells [49]. Clinically, it has been confirmed the MEG3 level is correlated with a sensitivity to oxaliplatin and cell apoptosis [50]. See **Table 4**.

Urothelial carcinoma associated 1 (UCA1)

Studies have confirmed that UCA1 is highly expressed in CRC tissues and is correlated with patient prognosis. UCA1 plays a role in promoting the cell cycle of CRC. Furthermore, it has been confirmed that UCA1 can decrease the anti-tumor effect and regulate the resistance of chemotherapy drugs by binding with miR-204-5p, which then leads to resistance to 5-FU in CRC [51-54]. See **Table 5**.

Other lncRNAs

LncRNAs are a kind of genetic information, and different fragments have similar or different functions. With the development of research, more and more lncRNAs related to CRC have been found. The latest ones include: lncRNA activated by TGF-β (LncRNA-ATB), ENST000-0054754, and LncRNA-2023. However, their

Table 1. HOTAIR and CRC

Author	Year of publication	Enrolled cases	Research results of HOTAIR and CRC
Xiao, et al.	2018	104	HOTAIR promotes the proliferation of CRC cells and promotes the development and chemotherapy resistance of CRC through the miR-203a-3p and Wnt/β-catenin signaling pathways.
Yang, et al.	2016	53	HOTAIR reduces the apoptosis of CRC cells. Silencing HOTAIR can inhibit the proliferation of CRC cells and increase their sensitivity to radiotherapy.
Svoboda, et al.	2014	171	High expressions of HOTAIR in CRC tissues are associated with a high risk of death, with a sensitivity of 67.12% and a specificity of 92.55%.
Zhao, et al.	2015	32	HOTAIR is highly expressed in the peripheral blood of CRC patients. The area under the curve (AUC) for the diagnosis of CRC is 0.777, 95% CI (0.663-0.891).

Note: CRC: Colorectal cancer.

Table 2. MALAT1 and CRC

Author	Year of publication	Enrolled cases	Research results of MALAT1 and CRC
Ji, et al.	2013	60	MALAT1 promotes tumor invasion and lymph node metastasis, which may be related to the Wnt/β-catenin signaling pathway. Resveratrol can block this pathway and inhibit the metastasis of CRC.
Li, et al.	2017	84	High expressions of MALAT1 were found in the tissues of CRC patients with metastasis. The clinical diagnostic efficacy was correlated with a sensitivity to oxaliplatin: sensitivity to oxaliplatin: sensitivity: 89.29%, specificity: 52.38%; insensitivity to oxaliplatin: sensitivity: 75.24%, specificity: 61.17%. MALAT1 may lead to a high expression of miR218 by activating the EZH2 and CDH1 genes, which then results in the drug resistance and distant metastasis.
Si, et al.	2017	96	MALAT1 may exert a cancer-promoting effect by activating autophagy, promoting cell proliferation, and inhibiting cell apoptosis through the miR-101 signaling pathway.
Xu, et al.	2018	40	MALAT1 may promote tumor proliferation and distant metastasis by accelerating the cell cycle and reducing the apoptosis of tumor cells by down-regulating miR-145 and up-regulating the SOX9 signaling pathway.
Wu, et al.	2019	78	MALAT1 is highly expressed in CRC tissues and may serve as a target for cancer metastasis intervention.

Note: CRC: Colorectal cancer; MALAT1: Metastasis-associated lung adenocarcinoma transcript 1.

Table 3. H19 and CRC

Author	Year of publication	Enrolled cases	Research results of H19 and CRC
Zhang, et al.	2017	94	H19 was used to diagnose CRC with a sensitivity of 78.95%, a specificity of 82.50%, and an AUC of 0.841. There is a positive correlation between TNM staging and H19 in CRC patients. H19 may promote the metastasis of cancer cells by up-regulating the expression of miR-675-5p.
Costa, et al.	2017	Cell experiments	H19 promotes the metastasis of CRC cells through the miR675/DDB2/EMT signaling pathway.
Chen, et al.	2017	24	H19 down-regulates the expression of VDR through the miR675 signaling pathway, and VDR regulates the expression of H19 through the C-Myc/Mad-1 signaling pathway, which promotes the progression of CRC.
Tsang, et al.	2010	30	High expressions of H19 and miR675 in CRC tissues may promote the proliferation of CRC cells through the H19/miR675/retinoblastoma (RB) signaling pathway.

Note: CRC: Colorectal cancer.

Table 4. MEG3 and CRC

Author	Year of publication	Enrolled case	Research results of MEG3 and CRC
Wang, et al.	2019	126	MEG3 was used to diagnose CRC with a sensitivity of 0.667, a specificity of 0.875, and an AUC of 0.798. The survival times of patients with high serum levels of MEG3 were longer than the survival times of patients with low serum levels of MEG3.
X. Dong, et al.	2018	84	The AUC for diagnosing CRC was 0.9384. The survival times of the patients with low serum levels of MEG3 were shorter.
Li, et al.	2017	140	MEG3 was used to diagnose CRC with a sensitivity of 0.739, a specificity of 0.614, and an AUC of 0.784. MEG3 can improve the sensitivity of CRC cells to chemotherapy by regulating cell apoptosis.
Yin, et al.	2015	62	MEG3 was positively correlated with the clinical tumor size, TNM staging, tissue invasion and long-term survival.

Note: MEG3: Maternally expressed gene 3; CRC: Colorectal cancer.

Table 5. UCA1 and CRC

Author	Year of publication	Enrolled cases	Research results of UCA1 and CRC
Sun, et al.	2019	32705	UCA1 was correlated with the size and depth of the invasion of CRC. It can decrease the sensitivity to radiotherapy and chemotherapy, promote cell proliferation and reduce the apoptosis of the tumor cells.
Bian, et al.	2016	90	UCA1 was significantly correlated with the poor prognosis of patients. It can cause resistance to 5-FU, which may be related to the inhibition of the function of miR-204-5p and the promotion of cancer cell proliferation.
Wang, et al.	2017	848	Patients with lymph node metastasis accompanied by high levels of UCA1 occur at a rate 2.07 times of those accompanied by low levels of UCA1. UCA1 can be used as a potential marker of lymph node metastasis of CRC.
Ni, et al.	2015	32	High levels of UCA1 are correlated with prognosis (lymph node metastasis, depth of invasion). They can increase the cell cycle (G0/G1), and decrease the apoptosis of cancer cells.

Note: CRC: colorectal cancer; CRC: urothelial carcinoma associated 1.

specific mechanisms are unclear, so further research is warranted [55].

Conclusion

LncRNAs, such as CCAT1, HOTAIR, CRNDE, NORAD and UCA1, can promote the metastasis of cancer cells by regulating the process of cell proliferation and apoptosis. There are also anti-neoplastic lncRNAs, like MEG3, which can inhibit cell proliferation and promote apoptosis. Moreover, lncRNAs such as MALAT1 are directly related to long-term prognosis. In clinical applications, CCAT1 and HOTAIR are mainly used in the diagnosis of CRC due to their high expressions in the peripheral blood, and CRNDE, UCA1, and MEG3 are used to provide important guidance in targeting chemotherapy intervention and drug resistance. However, these lncRNAs have not currently been used in the clinical diagnosis or prognostic evaluation of CRC, and the therapy targeted at lncRNAs is still being studied and has not been applied clinically.

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Disclosure of conflict of interest

None.

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