Review

The Biological Effect and Clinical Application of Long Noncoding RNAs in Colorectal Cancer

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Key Words

lncRNAs • Colorectal cancer • Tumorigenesis • Progression

Abstract

Colorectal cancer (CRC) is one of the most common malignancies in the world. Easier recurrence and metastasis is the main cause of mortality in CRC patients, and the markers applied for diagnosis and treatment of CRC is still urgently needed to early diagnose and evaluate therapeutic effect. Long noncoding RNA (lncRNA) is a class of noncoding RNA that the length is more than 200 nucleotides. With the development of sequencing technique about transcriptome, increasing lncRNAs are focused on their function and mechanism related to the nosogenesis and pathology of CRC. Recent studies report that lncRNAs acted as crucial role in CRC and could be as biomarker for CRC diagnosis and treatment. In this review, we display the regulation of lncRNA by interacting with DNA, RNA and protein and highlight the double role of lncRNAs as oncogene or anti-tumor gene involved in Wnt signaling pathway, p53 signaling pathway or others to be an regulator in CRC development. Lastly, we discuss some new finding of lncRNAs, especially lncRNA in exosome, which could be as potential markers for diagnosis and treatment of CRC in future.

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Introduction

Because of colorectal cancer (CRC) easily recurrence and metastasis, about 1.36 million new cases and 694,000 death cases were reported in every year [1]. In China, morbidity of CRC is on progressively increasing level and its mortality ranks the fifth of cancer-correlative death [2, 3]. Fundamentally, CRC is closely linked with dietary habit, genetic factor and disease factor, such as high fat and protein diet, family medical history, and chronic inflammation.

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Effect of CRC early screening showed high survival rate and low mortality in age of more 50 years old [4]. Therefore, it is very emergency to study pathogenesis of CRC and find one or more efficient biotargets to improve the survival quality of CRC patients [5, 6].

A previous study of human genome displayed that only 1.5%-2.0% genes of the whole genome were protein-coding genes (PCG), most of the others were performed transcription process and produced non-coding RNA (ncRNA) [7, 8]. lncRNAs, chiefly form by RNA polymerase II, are a class of ncRNAs with a length of more than 200nt and has no open reading frame (ORF) [9, 10]. Due to its long nucleotide chain and intricate secondary structure, lncRNAs could combine with protein by its multiple binding sites or specifically act on DNA or RNA by base pairing summarizing RNA-protein interplay, RNA-RNA base pairing and RNA-DNA base pairing [11]. Therefore, lncRNAs directly regulate gene expression on transcription, post transcription, and epigenetics level. Increasing reports suggested that lncRNAs, as a tumor regulator, were participated in complex network of biological regulation [12, 13]. Increasing lncRNAs were reported as the markers in CRC diagnosis, such as MALAT1, HOTAIR, H19 and CCAT [14-17]. Long non-coding RNA RP11-708H21.4 was identified to be down-regulated in CRC. Low expression level of RP11-708H21.4 was correlated with bad prognosis. Moreover, overexpressed RP11-708H21.4 play a role of tumor suppressor, which could enhance the sensitivity of 5-FU to colon cells [18]. In this review, we summarized a hot topic function and clinical application of lncRNAs which will be promising targets on diagnostics and therapy of CRC.

Regulation effect of lncRNAs

Similarly to mRNAs, lncRNAs has a construction with 5' cap and 3' poly A, and its forming process is involved in complicated cleaving pattern [11]. Based on sites relative to the protein-coding genes, lncRNAs are classified as intergenic lncRNAs, intronic lncRNAs, bidirectional lncRNAs, sense lncRNAs and antisense lncRNAs to act as regulators in tumor pathology [10]. Firstly, as cis-acting element or trans-acting element, lncRNAs contribute to control gene transcription. Moreover, lncRNAs also interact with protein to exert its function in gene regulation. One of the most famous cis-acting element is lncRNAs X-inactivation-specific transcript (Xist), which recruits polycomb repressive complex 2 (PRC2) leading to H3 acetylation and methylation, further inducing silence of whole X-chromosome [19, 20]. Recent study showed that long intergenic noncoding RNA p21 (lincRNA-p21) mediated p53 downstream gene [21]. The regulation of lincRNA-p21 belonged to hnRNP-K protein dependent transcriptional silencing and play a negative role in hindering expression of p53 downstream gene [22]. lncRNAs p53-induced noncoding RNA (PINCR) is another lncRNAs to regulate a subset of p53 targets. Binding to Matrin3 protein, PINCR is involved in enhancer region of these genes [23].

In addition, lncRNAs could interact with microRNA (miRNA) to regulate gene expression [24]. As we known, miRNAs exerts its function via targeting 3' UTR of mRNA [25]. Increasing studies demonstrated that lncRNAs played important roles in the regulation of miRNA. MD et al. summarized the four way of lncRNAs interacting with miRNAs, including acting as host gene to miRNAs, being instability by miRNAs, competing mRNA with miRNAs, trapping miRNAs [24]. The first interaction is that lncRNAs could be as the precursor sequence for miRNA. Through PriMir analysis, many lncRNAs are detected as host gene for miRNAs, such as PVT1 [26, 27]. Secondly, miRNAs could reduce the stability of lncRNAs. For example, Yoon et al. reported that let-7 family binded to RNA-binding protein (RBP) HuR for reducing the stability of long intergenic non-coding RNAs p21 [28]. Thirdly, lncRNAs is found to regulating the miRNAs expression to bind to miRNAs or its target. lncRNAs BACE1AS was reported to rob the target of miR-485-5p, BACE1, for relaxing the inhibition of BACE1 by miR-485-5p [29]. The last and common way is that lncRNAs, as competing endogenous RNAs (ceRNAs), play sponging roles to competitively bind to miRNAs for inhibiting binding activity. lncRNAs UCC could be interact with miR-143 by bioinformatics analysis, dual-luciferase reporter assays, and RNA immunoprecipitation, and UCC expression shows a negative relationship

with miR-143 in CRC [30]. Particularly, H19 has been identified in many studies acts as a miRNA decoy to bind miRNA and inhibit its activities in CRC, such as miR-138, miR-200a and miR-675-5p [31-33]. Hence, interaction of lncRNAs and miRNAs provide a new prospect to deeply understand lncRNAs-induced reactions involved in the pathogenesis and pathology of CRC.

Dysregulated lncRNAs in CRC

As we known, cancer capacity show infinite multiplication, invasion and metastasis, especially CRC. However, mechanism of cancer is more complicated than we imagined. Recently, sequencing technique is applied to detect transcriptome of cancer tissues including miRNAs and lncRNAs [34]. Increasing evidences found presence of dysregulated lncRNAs in various types of cancer, such as hepatic carcinoma, lung carcinoma and colorectal carcinoma controlled with its adjacent tissues [35-37].

It has been definite that lncRNAs play double roles in CRC. Some lncRNAs are upregulated, which adverse to CRC development, while the others were down-regulated, which contribute to CRC development.

The role of lncRNAs in CRC

The process of normal cells transformed into tumor is growingly developed related to multistage reaction and mutation accumulation. In this course, cancerous cells are increasingly away from the control by its normal regulating mechanism, which endows some new capacity and become cancer cells [38]. With the increasing of lncRNAs studies, more and more dysregulated lncRNAs were involved in regulating tumor progression [39, 40].

H19 was located on human chromosome 11 and was reported as regulator on cell growth and development [41]. It was detected up-regulated expression in CRC tissues. Survival analyses showed a significant poor prognosis in CRC patients with high H19 expression. Through verification of functional experiment, H19 was found as an oncogene to promote CRC cell proliferation [14]. Insulin-like growth factor 2 gene (IGF2), a paternal imprinted gene, was uniformly located on human chromosome 11 [42]. Study reported that differentially methylated region (DMR), which was located on H19 promoter upstream, could regulate IGF2 imprinting by aberrant DNA methylation [43, 44]. The link of H19 and IGF2 could affect tumor crucial activity by promoting DNA replication and hypermethylation on epigenetics [45, 46]. Recently, Lihua et al. found a novel lncRNAs, lnc34a, was notably upregulated in colon cancer stem cell (CCSC) lines and promoted CCSC self-renewing and tumorigenesis. Moreover, lnc34a recruit Dnmt3a via PHB2 and HDAC1 to target miR-34a by methylating and deacetylating its promoter to promote CRC cell proliferation [47]. Upregulated GAS5 reduced ability of cell proliferation, and promoted G0/G1 cell cycle arrest and apoptosis [48]. As we known, cancer cells always show apoptosis resistance under a variety of stress environment, such as oxygen deficit, denutrition, antitumor therapy [49]. Therefore, it was the reason that cancer cells could be survived by autophagy to mediate intracellular recycle of energy and metabolite [50]. Moreover, lncRNAs were reported that played important roles in regulating autophagy in cancer [51]. As previously mentioned, linc-POU3F3 was an oncogene that silencing linc-POU3F3 inhibited proliferation and migration, induced apoptosis in CRC. SMAD4, which is involved in TGF- β -induced autophagy, showed an increase because of linc-POU3F3 knockdown [52, 53]. In addition, autophagy related protein, BECLIN1, ATG5, ATG7, and LC3 II, were continually accumulated by linc-POU3F3 knockdown due to interdicted autophagy in CRC [53]. This study declared that linc-POU3F3 exerts its functional potential by mediating CRC autophagy. Recent study showed that dysregulated MEG3 also regulated tumor autophagy, tumorigenesis and progression, and further found that MEG3 had a negative related with an autophagy marker, microtubule-associated protein 1A/1B-light chain 3 (Atg8/LC3), Atg 3 [54]. Based on this, dysregulated MEG3 in CRC might induce autophagy by regulating autophagy key enzyme.

Moreover, malignant tumor always showed tumor metastasis, which is depended on neovascularization. The angiogenesis is a key process for forming new vessels to offer a guiding for tumor cell from primary site to remote organs [55]. This process is multidimensional that vascular endothelial cell (VEC) differentiates from existing vasculatures, migrates and forms new capillaries [55]. Tumor cell induces angiogenesis by liberating bioactive products to stimulate angiogenesis, such as vascular endothelial cell growth factor (VEGF), angiogenin (ANG), platelet derived growth factor (PDGF), transforming growth factor (TGF), fibroblast growth factors (FGF), which targeting VEC for increasing ability of proliferation. Then, variant VEC serves for tumor cell progression [56]. Recently clinical evidences demonstrated that dysregulated lncRNAs were significantly correlated with lymph node metastasis, tumor differentiation and TNM stage, especially vascular invasion in CRC [57, 58]. Following increasing evidences verified that angiogenesis was regulated by lncRNAs.

With the development of bioinformatics, sequencing technique and bioinformatic analyses are used to find more dysregulated lncRNAs and explore its potential biological function. Through analyzing lncRNAs and its regulated mRNA in colon cancer tissues, the data showed that a interaction with lncRNAs and mRNAs was involved in cellular activity of cell division, angiogenesis, apoptotic, et al. [59]. lncRNAs maternally expressed gene 3 (MEG3) was located on human chromosome 14. Differential expression analysis showed a low MEG3 expression level in diverse tumor, including CRC, and overexpression of MEG3 could inhibit CRC cell proliferation both *in vitro* and *in vivo* [54, 60]. Besides, increasing MEG3 expression not only restrained proliferation but also showed a negative effect on proliferation and angiogenesis in VEC. Through further study, MEG3 exerts its tumor suppression effect by playing a miRNA sponge to regulate miR-9 [61]. These studies above suggested that MEG3 might control double effect on inhibition of CRC proliferation by impeding angiogenesis in VEC.

Fig. 1. Signalling pathway of p53 by lncRNAs. Red arrows represented inhibition of p53 pathways; Green arrows indicated promotion of p53 pathways. Red rectangles indicated onco-lncRNAs. Violet rectangles represented suppressor of lncRNAs. Red rectangles indicated oncogene of lncRNAs. Purple rectangles indicated tumor suppressor of lncRNAs.

In addition, lncRNAs might be involved in certain molecular pathway to exert its regulation in CRC progression.

P53 signalling pathway

p53 was reported as a recognized tumor suppressor on inducing cell cycle arrest, apoptosis and other tumor behavior [62]. Cell cycle is one of essential feature in normal cells. However, tumor cells show inordinate cell cycle and this specific features offer unlimited reproduction to accelerate tumorigenesis and progression, which was involved in p53 regulatory mechanism [63, 64]. Some abnormal regulators, contain passionately reported lncRNAs, are the key to comprehend mechanism of tumorigenesis and progression (Fig. 1).

lncRNAs reprogramming (ROR) was reported as oncogene to facilitate CRC proliferation [65]. The deficiency of lncRNAs-ROR led to inhibition of cell proliferation, enhancement of cell apoptosis and motivation of cell cycle arrest in G0/G1 phase. There are increasing expressions of p53, p21 and FAS protein by downregulating lncRNAs-ROR in CRC. These findings suggested that lncRNAs-ROR played a tumor promoter by inhibiting p53 signaling way in CRC. Moreover, lncRNAs-ROR was reported as p53 upstream gene. Upregulated lncRNAs-ROR could weak radiosensitivity of CRC cells via sponging miR-145 and impeding p53 translation, play an inhibited role in radiotherapy effect to CRC [66].

Wnt/ β -catenin signalling pathway

Wnt/ β -catenin is a signaling involved in tumor development [67]. EMT, as a process of cell-cell adhesion, promotes tumor invasion and metastasis [68]. Among this pathway, β -catenin, which is a pivotal initial protein of Wnt signaling, is combined with E-cadherin to

Fig. 2. Signalling pathway of Wnt/ β -catenin by lncRNAs. Red arrows represented inhibition of Wnt/ β -catenin pathways; Green arrows indicated promotion of Wnt/ β -catenin pathways. Brown rectangles represented oncogene of lncRNAs. Green rectangles represented tumor suppressor of lncRNAs.

be as cytoskeletal protein effecting on cell motility [69, 70]. CTD903 was reported as a tumor suppressor that inhibited EMT phenotypes and CRC cell metastasis. After downregulating CTD903 expression, Wnt/ β -catenin expression, EMT-related protein expression (Vimentin, epithelial marker ZO-1) and its upstream transcriptional factors (Twist, Snail) were inhibited in CRC cell [71]. Differently, long non-coding RNA CCAL played an oncogenic role to CRC cell progression. Methylation and deacetylases of H3 provoked upregulated CCAL, further suppressing activator protein 2 α (AP-2 α), subsequently activated Wnt/ β -catenin signalling pathway. Specifically speaking, that overexpression of CCAL reduce AP-2 α expression and induce expression of β -catenin to target c-myc, cyclin D1 and E-cadherin. Besides, activation of Wnt/ β -catenin signalling pathway decreased MDR1/P-glycoprotein expression to involve in mechanism of CCAL on regulating CRC cell progression [72].

In addition to regulation of lncRNAs-protein, some miRNAs are contributed to mechanism of lncRNAs by Wnt/ β -catenin signaling pathway. lncRNAs CRNDE was reported in regulating CRC proliferation and migration of tumors by mediating Wnt/ β -catenin signaling, and as a ceRNA to bind to miR-217. Transcription factor 7-like 2 (TCF7L2) was the target of miR-217. CRNDE could competitively bind to miR-217 to increase TCF7L2 expression for activating Wnt/ β -catenin signaling. Moreover, CRNDE directly interacted with TCF7L2 to activate Wnt/ β -catenin signaling. Based on this study, CRNDE showed double effects on regulation of Wnt/ β -catenin signaling pathway [73]. Similarly, CCAT2 showed a tumor-promoting role on cancer growth, metastasis and chromosomal instability by interacting with TCF7L2 to regulate Wnt target genes. In turn, CCAT2 is reversely regulated by Wnt/ β -catenin signaling pathway due to regulation position of CCAT2 on Wnt downstream, which implied that there is a loop between CCAT2 and Wnt [74]. There were many reported lncRNAs involved in Wnt/ β -catenin signaling pathway (Fig. 2).

Other signalling pathways

RP11-708H21.4 was a novel low expressed lncRNAs in CRC. Overexpression of lncRNAs RP11-708H21.4 suppressed CRC cell proliferation through induction of G1 arrest and apoptosis, inhibition of CRC cell invasion. Through decreasing phosphorylation of AKT, mTOR, as well as S6K1, RP11-708H21.4 hindered AKT/mTOR pathway in CRC cells [18]. linc-POU3F3 was a novel biotarget in CRC, and knockdown linc-POU3F3 inhibited cell proliferation, migration and invasion in CRC cell lines, and promoted apoptosis by inducing G1 cell cycle arrest through change expression of cyclin D1, CDK4, p18, Rb, and phosphorylated Rb. SMAD4 was a key factor in BMP pathway, which influenced capacity of tumor metastasis. Silencing linc-POU3F3 led to increasing of SMAD4 and pSMAD1 expression to weak migration and invasion of CRC [53].

Clinical significance of lncRNAs for CRC

Increasing studies concentrated on diagnostic and therapeutic roles of lncRNAs in cancer. Ectopic lncRNAs always show a tissue and cancer specificity [75]. MALAT1, HOTAIR, H19 and CCAT family were reported as the markers in CRC diagnosis. H19 and HOTAIR was up-regulated, which implied a poor prognosis of high expression in CRC [14, 15]. The results of clinical features showed that H19 was associated with TNM-stage, tumour differentiation, HOTAIR with TNM-stage, tumour differentiation vessel invasion. Similarly, the FOXP4-AS1 and HOXA-AS2 showed onco-role in promoting CRC proliferation and apoptosis [16, 17]. These evidences displayed unfavourable prognostic markers for CRC patients. Oppositely, TUSC7 and GAS5 were downregulated and suggested a better prognosis of high expression level in CRC. The results of clinical features showed that TUSC7 was associated with tumor size, HOTAIR with tumor size and TNM-stage. In table 1, we concluded a correlation with CRC clinical features and lncRNAs for visually understanding that lncRNAs might be as markers for CRC diagnosis (Table 1) [16, 17, 47, 57, 75-80]. Sun et al. reported that ANRIL could enhance cell mobility and invasion by in-vitro tube formation HLECs invasion. When ANRIL were

Table 1. The expression and clinical characteristics of lncRNAs in CRC

LncRNAs	Chromosomal location	Gene types	Potential clinical significant	Tumor size	Tumour differentiation	CRC patient clinicopathologic features				References
						TNM-stage	Lymphatic metastasis	Distant metastasis	Vessel invasion	
H19	11p15.5	Oncogene	Tumor growth	/	*	*	/	/	/	[75]
HOTAIR	12q13.13	Oncogene	Metastasis and EMT	/	**	**	/	/	*	[57]
DANCR	4q12	Oncogene	Invasion and migration	/	/	*	*	/	/	[76]
CRNDE	16q12.2	Oncogene	Proliferation and chemoresistance	**	/	/	*	/	/	[77]
FOXP4-AS1	6p21.1	Oncogene	Proliferation and apoptosis	*	/	*	/	/	/	[16]
HOXA-AS2	7p15.2	Oncogene	Proliferation and apoptosis	**	/	**	**	/	/	[17]
NNT-AS1	5p12	Oncogene	Proliferation and migration	/	*	**	**	/	**	[78]
TUSC7	3q13.31	Tumor suppressor	Proliferation	*	/	/	/	/	/	[79]
GAS5	1q25.1	Tumor suppressor	Proliferation, G0/G1 arrest and apoptosis	**	/	*	/	/	/	[47]
ANRIL	9p21.3	Oncogene	Lymphangiogenesis and lymphatic metastasis	/	/	*	*	/	/	[80]

downregulated by gene interference, it is significant results that the rate of tumor growth and lymphatic metastasis and the frequency of transferred lymph nodes were reduced *in vivo*. Downregulated RP11-708H21.4 showed a correlation with poor prognosis, which artificial overexpressed RP11-708H21.4 could enhance the sensitivity of 5-FU to colon cells [18]. Currently, RNA interference (RNAi) technology was extensive to explore the function of gene. But, it still was limited due to its unknown side effect and stability to human. Does it induce other gene expression change? More animal experiment and clinical research need to be proved. Moreover, the upregulated lncRNA is more difficult than downregulated lncRNA expression due to less method, which implied a serious problem for tumor suppressor. Special chemical modification or stable vector was needed.

Recently, exosome is identified to transfer noncoding RNA for cancer diagnosis [82]. With the discovery of exosome, the lncRNA-faced dilemma was broken. RNA-Seq was used to identified transcriptome and long noncoding RNA sequencing from three extracellular vesicle subtypes in colon cancer LIM1863 cell line. 2, 389 mRNAs, 317 pseudogene transcripts, 1, 028 lncRNAs and 206 short non-coding RNAs were found in the exosomes released by LIM1863, which implied that the lncRNA is very enriched in LIM1863-excretive exosomes [83]. Moreover, Exosomal CRNDE-h is identified and stable in serum of CRC patients. High expression CRNDE-h was correlated lymph node metastasis ($P = 0.019$) and distant metastasis ($P = 0.003$) of CRC patients and has a lower overall survival rates (34.6% vs. 68.2%, $P < 0.001$) [84]. Therefore, lncRNA still has a potential in CRC diagnosis and therapy.

Conclusion

Recently, researchers try their best to find pathogenesis and nosetiology of CRC. With the development of bioinformatics, lncRNAs caught much attentions of numerous researchers and the landscape of lncRNAs functions were found in course of tumor development. To data, increasing number of lncRNAs had been reported that contributed to complex regulation network of development in CRC and showed potential role in CRC diagnosis and treatment. In this review, we summarized function and mechanism of lncRNAs involved in CRC progression, which will deep the understanding of lncRNAs regulation for further being a promising biomarkers and therapeutic targets for CRC patients.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (81560385), the Medical Scientific and Technological Research Project of Henan Province (201702027), Youth Innovation Fund Project of The First Affiliated Hospital of Zhengzhou University (YNQN2017035), and the China Postdoctoral Science Foundation (2017M610462).

Disclosure Statement

All authors have claimed that there is no existing conflict.

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