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Original Article

LncRNA, a novel target biomolecule, is involved in the progression of colorectal cancer

Weihong Sun, Shaoshao Ren, Ran Li, Qingshan Zhang, Haiping Song

Biotherapy Center, Department of Oncology, Qingdao Tumor Hospital, Second Affiliated Hospital of Medical College of Qingdao University, No. 127 Siliu South Road, Qingdao 266042, Shandong, China

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Abstract: Colorectal cancer is one of the most commonly diagnosed malignancies among males and females worldwide. Although China is a country with a low incidence of colorectal cancer, with the improvement of China's economy and lifestyle changes, the incidence rate in China has generally increased in recent years, and the morbidity and mortality of colorectal cancer rank fifth among those of all malignant tumours. Furthermore, despite recent improvements in screening strategies and treatments for colorectal cancer, the prognosis of advanced colorectal cancer is still poor, mainly due to the recurrence or distant metastasis of this disease. Thus, colorectal cancer still seriously threatens the health and life of people and is a major public health problem worthy of further study. Recently, accumulating evidence has revealed that colorectal carcinogenesis might be a multistep process driven by progressive genetic abnormalities, including changes in lncRNA expression. Moreover, a large number of studies have discovered and studied the abnormal expression of lncRNAs in colorectal cancer, providing a promising target for the diagnosis and treatment of colorectal cancer, which will promote human understanding of the pathogenesis of colorectal cancer and improve diagnosis and treatment. Therefore, in the present review, we mainly summarize the present status of colorectal cancer, the characteristics, functions and clinical perspectives of lncRNAs, and the current therapeutic methods used for colorectal cancer, especially the application of lncRNAs in the treatment of colorectal cancer. It is hoped that this review will give readers a new understanding of the roles of lncRNAs in colorectal cancer.

Keywords: Colorectal cancer, long non-coding RNAs (lncRNAs), radiation therapy, chemotherapy, small-molecule therapy

Introduction

Colorectal cancer

Cancer is a class of malignant disease that is characterized by uncontrolled cell proliferation, resistance to cell death and the ability to invade or migrate to other parts of the body by forming metastases, and it is the second cause of death affecting both men and women worldwide, following cardiovascular diseases [1]. Moreover, it has been estimated that the number of deaths due to cancers is expected to rise to 13.2 million in 2030 [2, 3]. Therefore, cancer has caused a large global economic burden and has had a remarkable impact on public health [4]. Among different types of cancers, human colorectal cancer has been ranked the third most frequently diagnosed malignancy worldwide and one of the leading causes of cancer-related mortality detected in Western countries, exceeded only by lung, liver and stomach cancers [5]. Current management strategies for colorectal cancer treatment mainly include surgery, chemotherapy, radiotherapy, and immunotherapy [6, 7]. Clinically, different treatment options are generally selected according to the state of the patient, the location, and stage of the colorectal cancer, patient age, and patient health [8]. Usually, patients with colorectal cancer have an excellent prognosis if the disease is diagnosed and surgically treated at an early stage (before metastasis), with surgery being the treatment of choice for patients with localized disease [9]. If colorectal cancer patients have entered the advanced stage, surgery is no longer the best treatment, and other treatments are given clini-

cally [10]. However, with the major advances in these treatment methods, the overall survival rate of colorectal cancer patients has been notably improved, but many adverse effects of these treatments still exist [11]. For example, multi-drug resistance sometimes causes chemotherapy failure; adverse reactions induced by chemotherapy or radiotherapy, such as chronic diarrhoea or intestinal obstructions, conspicuously reduce the quality of life of patients; and individual differences are also an important challenge for immunotherapy [12]. Moreover, the most important point is that these treatments do not prevent the recurrence and metastasis of colorectal cancer [13, 14]. In addition, the incidence of colorectal cancer has increased alarmingly in recent decades and will continue to increase in the future. Hence, significant efforts are urgently needed to understand colorectal carcinogenesis, but the underlying biological processes and pathogenesis mechanisms of colorectal cancer have still not been fully illuminated over the past several years [13].

On the basis of global epidemiological and scientific studies, several risk factors have been identified for colorectal cancer, such as sex, ethnicity, diet, obesity, older age, family history, genetic mutations, inflammatory processes, and the gut microbiota [15, 16]. Recent findings indicate that among these factors, genetic factors, especially non-coding RNAs (ncRNAs), might largely contribute to the progression of cancer and tumour formation [17]. Furthermore, a large amount of evidence has clearly reported that tumorigenesis is a multistep process that results from a stepwise accumulation of genetic and epigenetic alterations, eventually triggering the normal colonic epithelial cells to transform into cancer cells [18]. Thus, many investigators have devoted great efforts to exploring the biological functions of ncRNAs in the occurrence, development and progression of colorectal cancer in the past few decades. These studies will open up new avenues for screening strategies, early diagnosis, prognosis and subsequent development of targeted drugs for colorectal cancer [19].

Long non-coding RNAs (lncRNAs)

The Encyclopedia of DNA Elements (ENCODE) project, which is the most comprehensive effort yet for surveying transcription in human eukaryotic cells, has precisely revealed that most of the eukaryotic genome can be transcribed, with approximately 20,000~25,000 genes encoding proteins according to high-throughput genome-sequencing technologies, whereas the vast majority of untranslated fractions of the transcriptome (accounting for about 98% of the total human genome) are transcribed as ncRNAs, which were formerly regarded as spurious "garbage" or scrambled transcriptional "noise" for decades [20]. However, these ncRNAs have recently been considered a novel class of RNA molecules and have challenged the traditional central dogma [21]. Additionally, it was also found that ncRNAs could be involved in multiple biological processes by directly or indirectly interfering with gene expression, such as cell proliferation, cell fate determination, apoptosis, signal transduction, organ development, and cell differentiation, and even the pathogenesis of many human diseases, especially cancers [17, 21, 22]. Generally, ncRNAs can be systematically classified into two groups according to their product size: small ncRNAs (sncRNAs) and lncRNAs. The sncRNAs are usually shorter than 200 nucleotides (nt), and this group contains microRNAs (miRNAs), small interfering RNAs (siRNAs), small nucleolar RNAs (snoRNAs), small nuclear RNAs (snRNAs), PIWI-interacting RNAs (piRNAs), ribosomal RNAs (rRNAs), transfer RNAs (tRNAs), and other sncRNAs. LncRNAs are longer than 200 nt and include intergenic lncRNAs, intronic lncRNAs, bidirectional lncRNAs, sense lncRNAs and antisense lncRNAs, which are classified based on their genomic localization and orientation according to the neighbouring protein-coding gene) (shown in **Figure 1A**) [21, 23]. Among such a wide variety of ncRNAs, the potential roles of miRNAs and lncRNAs in the progression of cancers have received much attention from many investigators and have been extensively studied in recent years [24, 25]. For example, miR-155 regulates the proliferation and apoptosis of pancreatic cancer cells by targeting suppressor of cytokine signalling 3 (SOCS3) [26]. High expression of miR-155 is closely associated with the recurrence or metastasis of non-small-cell lung cancer [27]. The cell survival, growth, and chemosensitivity of breast cancer were modulated by miR-155 via direct targeting of forkhead box O3a (FOXO3a) [28]. Therefore, these studies sug-

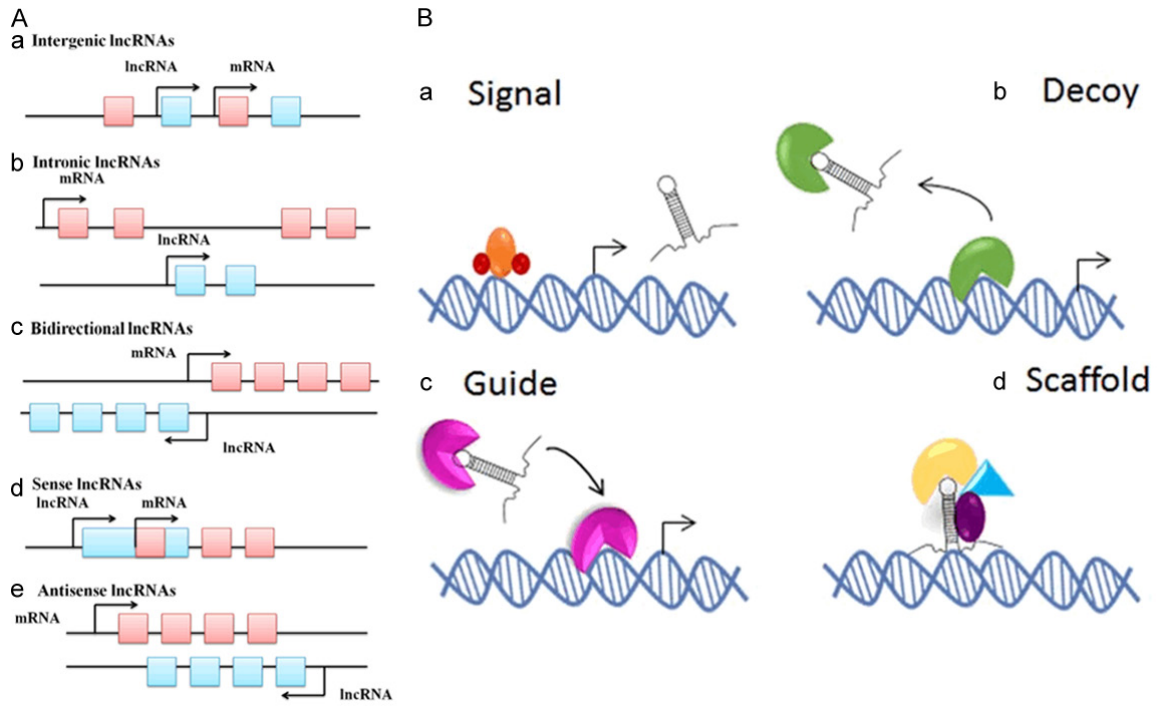

Figure 1. A. The classification of lncRNAs [37]. a. Intergenic lncRNAs: the entire sequence of the lncRNA falls between two protein-coding genes as a distinct unit; b. Intronic lncRNAs: the entire sequence of the lncRNA falls within the intron of a protein-coding gene; c. Bidirectional lncRNAs: the expression of the lncRNA and its neighbouring protein-coding genes on the opposite strand is initiated in close genomic proximity; d. Sense lncRNAs: lncRNAs are found inside or to the 5' side of a protein-coding gene and are transcribed in the same direction of protein-coding genes; these ultimately overlap at least one protein-coding exon; e. Antisense lncRNAs: lncRNAs are found inside or to the 3' side of a protein-coding gene and are transcribed in the opposite direction of protein-coding genes; these ultimately overlap at least one protein-coding exon. B. The biological roles of lncRNAs [38]. a. Signalling molecule: activate gene expression; b. Decoy molecule: suppress gene expression; c. Guide molecule: promote chromatin modification; d. Scaffold molecule: act on chromatin structure.

gest that miR-155 might function as an oncomiR gene in various cancers. Additionally, the lncRNA H19/miR-29b-3p regulatory axis participates in epithelial-mesenchymal transition and the metastasis of bladder cancer [29]; the lncRNA H19 promotes the progression of lung adenocarcinoma by directly targeting methylation-dependent repression of the cadherin 1 (CDH1) promoter [30], and H19 affects epithelial-mesenchymal transition and metastasis by regulating the STAT3/EZH2 axis in oesophageal cancer [31]. Therefore, these data indicate that H19 might exert a crucial role in various cancers. In fact, in the study of carcinogenesis, lncRNA has been more favoured by researchers than miRNA in recent years [24]. The lncRNA maternally expressed gene 3 (MEG3), which is located at the DLK1-MEG3 site of chromosome 14q32.3, was the first lncRNA discovered to inhibit tumour growth, and its discovery promoted a surge of research regarding the relationship between lncRNAs and cancers [32]. Compared with sncRNAs, lncRNAs have a more complex spatial structure; therefore, lncRNAs can positively or negatively play a regulatory role in protein-RNA, RNA-RNA and RNA-DNA interactions through their special secondary and tertiary spatial structures [23]. In addition, compared with the protein-coding genes, although lncRNAs are expressed at a lower level, they have more tissue specificity and temporal specificity, and they are expressed in both the nucleus and the cytoplasm [33]. Moreover, lncRNAs are involved in every aspect of biological activity, from the growth and development of organisms to the proliferation and differentiation of cells, endocytosis, and neurotransmitter transmission [34]. Therefore, lncRNAs have potential future clinical implications in terms of diagnosis, prognosis and therapeutic strategies for cancer patients.

In the past decade, advances in genome sequencing and analysis have made the discovery of tens of thousands of lncRNAs easier, and the process of lncRNA biogenesis was also revealed [35]. First, most lncRNAs can be transcribed from intergenic, exonic or distal protein-coding regions of the genome by the enzyme RNA polymerase II, and only a small portion of them are synthesized by the RNA polymerase III (Pol III) complex or the single-polypeptide nuclear RNA polymerase IV (spRNAP IV) complex. Second, the pre-mature lncRNA undergoes 5'-capping with methyl-guanosine, takes on a multi-exonic structure and undergoes 3'-polyadenylation. Third, lncRNAs continue to undergo alternative splicing modifications and RNA editing procedures to generate diversity. Finally, mature lncRNAs are released and transported to subcellular locations based on their functions [36]. Currently, it was concluded that lncRNAs can carry out their functions in four different ways, namely, as signals, decoys, guides, and scaffolds (**Figure 1B**) [24]. As a signal molecule, lncRNA is an indicator of transcriptional activity, which can activate or deactivate the natural functions of target proteins. As a decoy molecule, lncRNA can negatively regulate an effector by preventing the access of regulatory proteins to DNA. As a guide molecule, lncRNA is required for the proper localization of specific proteins, a process that is closely associated with cancer-related gene expression and can ultimately cause the formation of cancers. As a scaffold molecule, lncRNA is equal to an adaptor or an assembly platform to bind two or more protein partners and serves a structural role [23]. Hence, the multifunctional regulatory mechanisms of lncRNAs, their roles in human diseases, and their potential diagnostic and therapeutic applications will become the future research directions of researchers [33].

LncRNAs and colorectal cancer

According to preliminary statistics, approximately 90% of colorectal cancers are sporadic, and only a few cases (<10%) are hereditary [39]. Furthermore, there is growing evidence that colorectal cancer is a result of multiple factors and multiple gene interactions, and variations in molecular signalling pathways exert an essential role during the occurrence and development of colorectal cancer [40, 41]. Although the current research on the molecular signalling pathways of colorectal cancer has made some progress, the underlying mechanisms of colorectal cancer during its occurrence, development and metastasis still cannot be explained [42]. However, in recent years, with the rise in lncRNA research, the mystery of lncRNA has also been gradually revealed [24]. Although lncRNAs cannot directly encode the synthesis of proteins, they are closely related to the regulation of gene expression at the epigenetic level, transcriptional level and post-transcriptional level, and they have been shown to participate in the occurrence and development of colorectal cancer [43].

LIT1/KCNQ1OT1 was detected for the first time in the genome of patients with colorectal cancer and was the first lncRNA discovered in colorectal cancer [44]. Since then, an increasing number of studies have focused on lncRNAs that are differentially expressed during the pathogenesis of colorectal cancer, and some specific lncRNAs associated with the biological processes and clinical aspects of colorectal cancer have been gradually identified [42]. For instance, the lncRNA CTA-941F9.9 is frequently found to be downregulated and may be regarded as a biomarker for carcinogenesis in colorectal cancer [45]; the lncRNA FYVE, RhoGEF and PH domain-containing 5 antisense RNA 1 (FGD5-AS1) accelerates cell proliferation, migration, and invasion via sponging miR-302e as an endogenous competing mechanism and further upregulating cell division cycle-associated 7 (CDCA7) in colorectal cancer [46]; the lncRNA small nucleolar RNA host gene 6 (SNHG6) inhibits cell proliferation and metastasis by targeting ETS proto-oncogene 1 (ETS1), which then regulates the PI3K/AKT/mTOR pathway to play a role in colorectal cancer [47]; the lncRNA SLCO4A1-AS1 promotes colorectal cancer cell proliferation by enhancing autophagy via the miR-508-3p/partition-defective 3 (PARD3) axis [48]; and the lncRNA zinc finger antisense 1 (ZFAS1) participates in biological processes in colorectal cancer, such as cell proliferation, migration, invasion, and apoptosis, by mediating miR-7-5p [49]. In addition, many lncRNAs have been found to play a role in the initiation, progression and metastasis of colorectal cancer (as illustrated in **Table 1**) [24, 36, 43]. Thus, the pathophysiological significance of lncRNAs in colorectal cancer is

Table 1. Expression of lncRNAs associated with human colorectal cancer

LncRNAs	Location	Expression	Samples or models	Function in tumorigenesis	References
ADAMTS9-AS2 (ADAMTS9 antisense RNA 2)	Chromosome 3	Decreased	Colorectal cancer patients	ADAMTS9-AS2 overexpression in colorectal cancer cells inhibited cell proliferation, migration, and invasion, while suppression of ADAMTS9-AS2 showed opposite effects.	[50]
CCAL (colorectal cancer-associated lncRNA)	NA	Increased	Colorectal cancer cell lines	CCAL transferred from fibroblasts via exosomes strengthens chemoresistance in colorectal cancer cells.	[51]
CCAT1 (colon cancer-associated transcript-1)	8q24.21	Decreased	Colorectal cancer patients	CCAT1 exerts an essential role in the genesis, development, invasion and metastasis of colorectal cancer, and it also mediates epithelial-mesenchymal transition (EMT) in colorectal cancer.	[52]
CCAT1-L (colon cancer-associated transcript-1 ligand)	8q24	Increased	Colorectal cancer patients	Lower CCAT1-L decreased the long-range interactions between the MYC promoter and its enhancers. Meanwhile, CCAT1-L also acted on CTCF and further changed the chromatin conformation at these loop regions.	[53]
CCAT2 (colon cancer-associated transcript-2)	8q24.21	Increased	Colorectal cancer patients and cell lines	CCAT2 played a crucial role in colorectal cancer pathogenesis through regulating MYC and WNT, which could provide an alternative explanation of the SNP-conferred cancer risk.	[54]
CRNDE (colorectal neoplasia differentially expressed)	16q12.2	Increased	Colorectal cancer patients and cell lines	The CRNDE/miR-181a-5p regulatory axis motivated cell proliferation and chemoresistance in colorectal cancer by modulating the Wnt/β-catenin signalling pathway.	[55]
CTA-941F9.9	NA	Decreased	Colorectal cancer patients and cell lines	CTA-941F9.9 was discovered to be reduced in colorectal cancer compared with expression in non-tumour adjacent tissues and was speculated to be involved in colorectal cancer carcinogenesis.	[45]
DUXAP8 (double homeobox A pseudogene 8)	Chromosome 22	Increased	Colorectal cancer patients and cell lines	The STAT3-induced upregulation of the lncRNA DUXAP8 functioned as a ceRNA for miR-577 to facilitate tumour metastasis in colorectal cancer through the regulation of RAB14.	[56]
FGD5-AS1 (FGD5 antisense RNA 1)	3p25.1	Increased	Colorectal cancer cell lines	FGD5-AS1 accelerated colorectal cancer progression through forming a miR-302e sponge, which further regulated its downstream target CDCA7.	[46]
FOXP4-AS1 (FOXP4 antisense RNA 1)	Chromosome 6	Increased	Colorectal cancer patients and cell lines	FOXP4-AS1, which is considered an unfavourable prognostic factor, triggered cell proliferation and apoptosis in colorectal cancer.	[57]
GAS5 (growth arrest-specific 5)	1q25.1	Decreased	Colorectal cancer patients and cell lines	The lncRNA GAS5 promoted PTEN expression by functioning as a competing endogenous RNA (ceRNA) of miR-222-3p, thus inhibiting cell metastasis and promoting cell autophagy during the development of colorectal cancer.	[58]
GLCC1	NA	Increased	Colorectal cancer patients	GLCC1 protected c-Myc transcriptional factors from ubiquitination by directly acting on the HSP90 chaperone, which further altered the transcriptional pattern of c-Myc target genes, such as LDHA, and consequently reprogrammed the glycolytic metabolism of colorectal cancer cell proliferation.	[59]
H19 (human homologue 19)	11p15.5	Increased	Colorectal cancer patients and cell lines	Abnormal H19 expression resulted in EMT of colorectal cancer cells by mediating the miR-29b-3p/PGRN axis and continuing to act on Wnt signalling.	[60]
HNF1A-AS1 (HIF1A antisense RNA 1)	Chromosome 14	Increased	Colorectal cancer cell lines	HNF1A-AS1 has been reported to be involved in carcinogenesis via activation of the Wnt/β-catenin signalling pathway, which indicates a poor prognosis in colorectal cancer.	[61]
HOTAIR (HOX transcript antisense RNA)	12q13.13	Increased	Colorectal cancer patients and cell lines	HOTAIR participated in the progression and chemoresistance of colorectal cancer via increasing miR-203a-3p expression and activating the Wnt/β-catenin signalling pathway.	[62]
ITGB1 (integrin subunit beta 1)	Chromosome 10	Increased	Colorectal cancer patients and cell lines	ITGB1 enhanced colorectal cancer cell migration and invasion via upregulating BDNF.	[63]
LINC02418 (long intergenic non-protein-coding RNA 2418)	12q24.33	Increased	Colorectal cancer patients	LINC02418 served as a ceRNA to further promote MELK expression through sponging miR-1273g-3p and might serve as a diagnostic marker for colorectal cancer.	[64]
MALAT1 (metastasis-associated lung adenocarcinoma transcript 1)	11q13.1	Increased	Colorectal cancer patients and cell lines	MALAT1 triggered autophagy, facilitated cell proliferation, and hindered apoptosis by sponging miR-101 in colorectal cancer cells.	[65]
MEG3 (maternally expressed gene 3)	14q32.2	Increased	Colorectal cancer patients	MEG3 controlled cellular biological functions by directly regulating adenosine deaminase's effect on RNA 1 in colorectal cancer.	[66]

MIR17HG (miR-17-92a-1 cluster host gene)	Chromosome 13	Increased	Colorectal cancer patients and cell lines	MIR17HG promoted colorectal cancer progression via miR-17-5p and played an oncogenic role in colorectal cancer.	[67]
MIR503HG (MIR503 host gene)	Chromosome X	Decreased	Colorectal cancer cell lines	Forced MIR503HG expression suppressed colorectal cancer cell migration and invasion mediated by TGF-β2.	[68]
PRNCR1 (prostate cancer-associated non-coding RNA 1)	8q24.21	Increased	Colorectal cancer cell lines	PRNCR1, a potential oncogene, accelerated cell proliferation in colorectal cancer.	[69]
PVT-1 (Pvt1 oncogene)	8q24	Increased	Colorectal cancer cell lines	PVT-1 might be a prognostic indicator for colorectal cancer patients based on its antiapoptotic activity in colorectal cancer.	[70]
RHBDD1 (rhomboid domain-containing 1)	Chromosome 2	Increased	Colorectal cancer patients	RHBDD1 caused tumour metastasis via activating the Wnt signalling pathway and its downstream target ZEB1 in colorectal cancer.	[71]
ROR1-AS1 (ROR1 antisense RNA 1)	1p31.3	Increased	Colorectal cancer patients and cell lines	Triggering of the Wnt/β-catenin signalling pathway by ROR1-AS1 enhanced cell metastasis and proliferation in colorectal cancer.	[72]
RUNX1-IT1 (RUNX1 intronic transcript 1)	Chromosome 21	Decreased	Colorectal cancer cell lines	RUNX1-IT1, as a tumour-suppressive gene, participated in the progression of colorectal cancer by restraining cell proliferation and migration.	[73]
SLCO4A1-AS1 (SLCO4A1 antisense RNA 1)	20q13.33	Increased	Colorectal cancer cell lines	SLCO4A1-AS1 induced autophagy via mediating the miR-508-3p/PARD3 axis, which ultimately promoted colorectal cancer cell proliferation.	[48]
SNHG6 (small nucleolar RNA host gene 6)	Chromosome 8	Increased	Colorectal cancer cell lines	SNHG6 directly enhanced the TGF-β/Smad signalling pathway via targeting UPF1 and promoted EMT via regulation of ZEB, which ultimately led to cell proliferation, invasion and migration in colorectal cancer.	[74]
SNHG14 (small nucleolar RNA host gene 14)	Chromosome 15	Increased	Colorectal cancer patients	The SNHG14/hsa-miRNA-3940-5p/NAP1L2 axis had more advantages than CEA or CA19.9 in differentiating colorectal cancer from controls.	[75]
SH3PXD2A-AS1 (SH3PXD2A antisense RNA 1)	Chromosome 10	Increased	Colorectal cancer patients and cell lines	SH3PXD2A-AS1 facilitated cancer progression partly by the targeted inhibition of P57 and KLF2 expression in colorectal cancer.	[76]
TP73-AS1 (TP73 antisense RNA 1)	Chromosome 1	Increased	Colorectal cancer patients and cell lines	TP73-AS1 directly bound miR-194 and accelerated cell proliferation, migration and invasion via elevating TGF-α expression in colorectal cancer.	[77]
TUG1 (taurine upregulated 1)	Chromosome 22	Increased	Colorectal cancer cell lines	TUG1 upregulated KIAA1199 expression by sponging miR-600, which further promoted cell metastasis and epithelial-mesenchymal transition in colorectal cancer.	[78]
XIRP2-AS1 (XIRP2 antisense RNA 1)	2q24.3	Decreased	Colorectal cancer patients and cell lines	XIRP2-AS1 impeded cell proliferation and invasion by targeting miR-182 in *in vitro* and *in vivo* models. Moreover, the clinical sample analysis showed that XIRP2-AS1 might be a favourable factor for evaluating the overall survival and progression-free survival of patients with colon cancer.	[79]

undoubtedly an important future research direction [16]. At the same time, detecting and identifying the lncRNAs with potential functions in colorectal cancer are the only way to study lncRNAs, and these processes are a prerequisite for the use of lncRNAs in the diagnosis and treatment of tumours.

Treatment strategies for colorectal cancer

Colorectal cancer, originating from the colon and the rectum, represents a serious health concern, with approximately one million new cases of colorectal cancer diagnosed worldwide, and half a million people dying from colorectal cancer every year [16]. Although there has been a dramatic improvement in the survival rates of colorectal cancer in the past 10 years due to the development of new therapeutic strategies, the incidence of colorectal cancer still remains high [6, 15]. Thus, the treatment strategies for colorectal cancer have always been an area of interest for clinicians [10]. Recently, holistic treatment options, including surgery, radiation therapy, chemotherapy, immunotherapy, and targeted drugs, have been established [41, 80]. In addition, small-molecule therapy programmes are also gradually emerging [18, 19].

Surgery, radiation therapy, and chemotherapy

At present, the treatment of colorectal cancer is still based on surgery, and surgical treatment is also recognized as the only way to cure colorectal cancer for patients who are diagnosed early (who have an excellent prognosis) [9]. Although we have not seen breakthroughs in the field of surgery in the past few years, surgeons have thoroughly compared existing surgical methods [81]. We have evolved from traditional open surgery to a variety of surgical procedures, including endoscopic surgery, laparoscopic surgery, transanal total mesorectal excision, and robotic surgery [81, 82]. After a large number of clinical studies have obtained similar oncology and survival outcomes, surgeons will focus on controlling surgical complications and improving postoperative quality of life [83]. In addition to surgical treatment, radiotherapy is the most effective and valuable treatment for local and non-metastatic colorectal cancer patients but is inefficient when the cancer has spread throughout the body [84, 85]. If regional or distant metastases are discovered at the time of diagnosis, clinicians may use surgery combined with other treatments, such as chemotherapy [86]. Chemotherapy, as the major therapeutic strategy, mainly utilizes different drugs or drug combinations and delivers these drugs to the metastatic site to further inhibit the rapid proliferation of cancer cells or reduce cancer cell division [87]. However, due to the inhibition of cell growth, which is required for the maintenance of hair follicles, bone marrow and gastrointestinal tract cells, patients ultimately suffer from unwanted side effects, such as hand-foot syndrome, diarrhoea, gastrointestinal toxicity, mucositis, anaemia, neutropenia, vomiting, nausea, fatigue, haematologic disorders and liver toxicity [88, 89]. Moreover, with the frequent use of chemotherapy drugs, drug resistance has also emerged, which leads to limited chemotherapy efficacy [90]. As such, to overcome the underlying side effects, better treatment options for colorectal cancer urgently need to be explored.

Immunotherapy

With the rapid development and cross-infiltration of related disciplines such as oncology, immunology and molecular biology, research on tumour immunotherapy has advanced by leaps and bounds [91]. Immunotherapy has become an important treatment for cancer after surgery, radiotherapy and chemotherapy [91, 92]. Currently, immunotherapy methods for colorectal cancer mainly include cancer vaccines, cell therapy, cytokine treatment, and immunological checkpoint inhibitor treatment [93]. Cancer vaccines enhance and improve the killing effect of the immune system on tumour cells by regulating the interaction between antigen-presenting cells and T lymphocytes [94]. To date, cancer vaccines for colorectal cancer have consisted of whole tumour cell vaccines, peptide vaccines, DNA vaccines, dendritic cell (DC) vaccines, and viral vector vaccines [95]. Cellular therapy, also known as adoptive cellular immunotherapy (ACT), uses external T cells to influence the ability of patient T cells to specifically recognize tumour cells, thereby producing a killing effect on tumour cells. Widely studied immune effector cells include autologous lymphokine-activated killer (LAK) cells, autologous tumour-infiltrating lymphocytes (TILs), natural killer (NK) cells, cytotoxic T lymphocytes (CTLs), and

genetically modified T cells, such as chimeric antigen receptor (CAR) T cells, and T cell receptor chimeric (TCR) T cells [96]. In regards to cytokine treatment, cytokines are pleiotropic proteins that effectively activate tumour immune cells and fight tumour immune suppression [97]. They play key roles in all aspects of innate and specific immune responses and can kill tumour cells by activating the body's immune system and can also directly interfere with tumour cell proliferation. Studies have confirmed that cytokines that have inhibitory effects on gastrointestinal malignancies include interleukins (such as IL-2, IL-15, and IL-21), interferons (such as IFN-γ and IFN-α), and granulocyte-macrophage colony-stimulating factor (GM-CSF) [98]. An immune checkpoint refers to protein molecules expressed on tumour cells and/or immune cells that can regulate the initiation/activation processes of T cells [99]. Presently, inhibitory checkpoints have been found to include programmed cell death protein 1 (PD-1), PD-1/2 ligands (PD-L1/2), cytotoxic T lymphocyte antigen 4 (CTLA-4), lymphocyte activation gene 3, B/T lymphocyte-weakening factor, T cell immunoglobulin and mucin 3 [99, 100]. These co-suppressor molecules can induce T cell apoptosis and inhibit the function of activated T cells, while tumour cells can use this inhibition of the immune system to escape the specific killing effect of immune cells in the tumour microenvironment [100]. Immunological checkpoint inhibitors that have been recently approved by the Food and Drug Administration (FDA) for the treatment of malignant tumours include anti-PD-1 antibodies (e.g., nivolumab and pembrolizumab), anti-PD-L1 antibodies (e.g., atezolizumab, avelumab and durvalumab), and anti-CTLA-4 antibodies (e.g., ipilimumab), but there are few immunological checkpoint inhibitors that can be used for colorectal cancer treatment or that have demonstrated efficacy in clinical trials. In fact, with the development of modern medicine, immunotherapy has gradually become an area of interest for cancer treatment; immunotherapy is also a new direction for the treatment of colorectal cancer and has improved the prognosis of some patients to some extent [101]. However, the existing immunotherapy regimen in colorectal cancer shows a good immune response rate in only some subtypes of colorectal cancer, and most patients still have a low immune response rate. Multi-centre, large-sample-size studies are needed to increase the effectiveness and safety of immunotherapies in colorectal cancer patients, which could make more patients obtain more benefits [102]. Hence, colorectal cancer immunotherapy is a very promising treatment option and deserves further research and exploration.

Targeted drugs

With the advancements in tumour biomedicine, especially the development of tumour-targeted therapies and individualized precision therapies based on genotyping, patients with advanced colorectal cancer are expected to receive further benefits [103]. Targeted treatments are aimed at blocking specific biologic transduction pathways or proteins that are involved in tumour growth and tumour metastasis and are altered (i.e., upregulated, downregulated or mutated) in cancers [104]. At present, the reason why targeted therapy is so favoured by researchers is mainly because targeted therapy has unique advantages compared to other treatments, such as minimizing the death of normal cells, avoiding undesirable side effects, and carrying low toxicity and high efficacy [105]. Epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR) were the first protein targets developed by researchers [106]. Suppressing EGFR regulates tumour cell proliferation, invasion, metastasis, and tumour cell apoptosis via mediating the Ras/Raf/MEK/ERK-MAPK or PI3K/AKT/mTOR signalling pathways, while suppressing VEGFR promotes neovascularization, which can further provide nutrients for the proliferation of tumour cells [106].

A large number of studies have indicated that overexpression of EGFR is observed in colorectal cancer [107]. Cetuximab is a monoclonal antibody to EGFR that inhibits tumour cell proliferation, angiogenesis and metastasis, induces apoptosis, and hinders tumour growth. Therefore, cetuximab can be used to treat colorectal cancer at an advanced stage [108]. Studies have confirmed that cetuximab is more effective in RAS wild-type primary tumours located on the left side of the body than in metastatic colorectal cancer [109]. Additionally, panitumumab, which is a fully humanized, high-affinity IgG2 monoclonal antibody, can directly

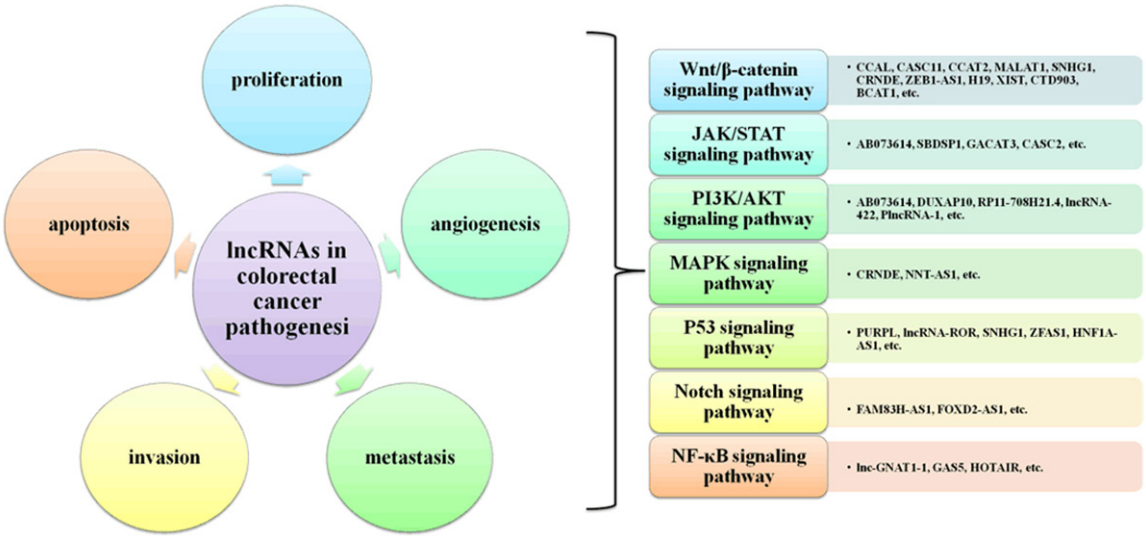

Figure 2. LncRNAs involved in the formation of colorectal cancer.

recognize EGFR [108]. Compared with cetuximab, panitumumab has a higher affinity for EGFR, a longer half-life and less allergic reactions [110]. Furthermore, it has been reported that panitumumab is not inferior to cetuximab in the treatment of patients with refractory KRAS wild-type metastatic colorectal cancer [110, 111]. Activation of VEGFR can trigger vascular endothelial cell proliferation, differentiation, and tumour cell infiltration; thus, blocking the VEGFR-mediated signalling pathway might suppress tumour growth [112]. Bevacizumab is a recombinant humanized IgG1 monoclonal antibody that specifically blocks VEGFR, attenuates its binding to endogenous VEGFR, inhibits endothelial cell proliferation and tumour angiogenesis, and eventually inhibits tumorigenesis [113]. Compared with cetuximab, bevacizumab was not associated with RAS mutation status [114]. In addition, apatinib is a small-molecule anti-angiogenic drug that competes with for the ATP-binding site of VEGFR-2 in cells, blocks downstream signal transduction, and inhibits tumour neovascularization [115]. Accumulating evidence has demonstrated that apatinib is safe and effective in phase II and III clinical studies of various solid tumours, such as advanced gastric cancer, colorectal cancer, and lung cancer [116]. There have also been many therapeutic drugs developed to inhibit EGFR (i.e., trastuzumab, pertuzumab, trastuzumab-emtansine, and lapatinib) and VEGFR (i.e., bevacizumab, ramucirumab, sorafenib, and sunitinib) [107, 112]. Moreover, nanocarriers, colloidal nano-scale systems capable of transporting anticancer agents, are emerging strategies in indirect cancer-targeted therapy [117]. With the in-depth study of the pathogenesis of colorectal cancer, more drugs may be developed for targeted therapy to achieve effective treatment of colorectal cancer in the future.

Small-molecule therapy

Ever since the discovery of lncRNAs, there is growing evidence that lncRNAs can be more exquisitely controlled and are restricted to specific cell types to a greater degree than mRNAs; therefore, lncRNAs have been regarded as potential markers for the diagnosis and treatment of colorectal cancer [6, 18]. Moreover, the functions of some lncRNAs in colorectal cancer pathogenesis have been identified (shown in **Figure 2**) [19, 42]. The Wnt/β-catenin signalling pathway, the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signalling pathway, the PI3K/AKT signalling pathway, the MAPK cascade, the p53 pathway, Notch signalling, nuclear factor κB (NF-κB) signalling, and other pathways participate in the pathogenesis of colorectal cancer via regulating cell proliferation, angiogenesis, metastasis, invasion and apoptosis, which are important events involved in the formation of colorectal cancer [5, 118]. In fact, uncontrolled proliferation, migration, invasion, metastasis, and

apoptosis are the main causes of failure in the treatment of colorectal cancer [119, 120]. However, numerous lncRNAs participate in tumour proliferation, migration, invasion and metastasis in colorectal cancer [120, 121]. Therefore, these dysregulated lncRNAs may be directly targeted by new drugs for colorectal cancer [121]. Small-molecule therapy, especially for the treatment of lncRNAs, will enable individualized treatment of colorectal cancer patients in the future [24, 122].

Conclusion

Colorectal cancer is one of the most common deadly cancers worldwide [16]. The incidence rate in China is generally on the rise, and the morbidity and mortality rate rank fifth among those of all malignant tumours [6, 15]. Presently, the treatment of colorectal cancer is mainly surgery, and with the advancement of surgical techniques, especially the extensive application of total mesorectal excision, the recurrence rate and mortality of colorectal cancer have been greatly reduced [10, 80]. However, local anatomy, lymphatic drainage, and tumour biological features of colorectal cancer limit the prospects of surgical techniques in improving patient outcomes and long-term survival [9, 104]. Therefore, the treatment of colorectal cancer tends to emphasize the multi-disciplinary, comprehensive treatment of surgically resected tumours, including radiotherapy, chemotherapy, immunotherapy and traditional Chinese treatments, which are mainly for improving the rate of surgical resection and reducing the rates of recurrence and mortality [104]. In recent years, with the clinical application of antibody drugs and anti-angiogenic drugs, therapeutic effects in colorectal cancer have been significantly improved; but in the treatment of patients with advanced-stage disease, postoperative recurrence and chemotherapy resistance are still difficult points, and the prognosis of these patients remains very poor, which seriously affects the quality of life of patients and causes significant economic losses to patients' families and national health insurance funds [102]. Despite continuous research on the risk factors, pathogenesis, diagnosis, treatment and prognosis of colorectal cancer in recent years, the molecular and genetic mechanisms of colorectal cancer are still not fully understood, and therapeutic effects have not been satisfactory [39]. These shortcomings are considered to be the result of a combination of environmental factors and genetic characteristics [2]. Multiple factors, such as activation of tumour susceptibility genes, inactivation of tumour suppressor gene, abnormal regulation of signalling pathways and the complexity of ncRNA regulation of protein-coding genes, are highly related to the development of colorectal cancer [17]. Among these factors, the deregulation of lncRNAs is regarded as an important change during the carcinogenesis of colorectal cancer [18, 24]. At the same time, growing evidence has demonstrated that lncRNAs can promote or inhibit the generation of colorectal cancer at different levels and through different mechanisms of action [42]. Thus, in this review, we summarized the functions of identified lncRNAs in the pathogenesis of colorectal cancer. Moreover, based on the roles of lncRNAs, the therapeutic potential of lncRNAs has become a new area of interest for research, which will open new directions for the treatment of colorectal cancer and bring new hope to patients with colorectal cancer. Nevertheless, it is undeniable that although lncRNAs may bring accurate treatment to patients with colorectal cancer, they still have certain challenges in that lncRNAs that are successful in cell and animal models do not necessarily translate into the clinic. In conclusion, further comprehensive study of lncRNAs will probably provide the ultimate solution for colorectal cancer diagnostics and therapeutics.

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Disclosure of conflict of interest

None.

Address correspondence to: Haiping Song, Department of Oncology, Qingdao Tumor Hospital, Second Affiliated Hospital of Medical College of Qingdao University, No. 127 Siliu South Road, Qingdao 266042, Shandong, China. Tel: +86-0532-84962202; Fax: +86-0532-84863506; E-mail: qdzlyynyk@163.com

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