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Diagnostic and prognostic potential of tissue and circulating long non-coding RNAs in colorectal tumors

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Abstract

Long non-coding RNAs (lncRNAs) are members of the non-protein coding RNA family longer than 200 nucleotides. They participate in the regulation of gene and protein expression influencing apoptosis, cell proliferation and immune responses, thereby playing a critical role in the development and progression of various cancers, including colorectal cancer (CRC). As CRC is one of the most frequently diagnosed malignancies worldwide with high mortality, its screening and early detection are crucial, so the identification of disease-specific biomarkers is necessary. lncRNAs are promising candidates as they are involved in carcinogenesis, and certain lncRNAs (e.g., CCAT1, CRNDE, CRCAL1-4) show altered expression in adenomas, making them potential early diagnostic markers. In addition to being useful as tissue-specific markers, analysis of circulating lncRNAs (e.g., CCAT1, CCAT2, BLACAT1, CRNDE, NEAT1, UCA1) in peripheral blood offers the possibility to establish minimally invasive, liquid biopsy-based diagnostic tests. This review article aims to describe the origin, structure, and functions of lncRNAs and to discuss their contribution to CRC development. Moreover, our purpose is to summarise lncRNAs showing altered expression levels during tumor formation in both colon tissue and plasma/serum samples and to demonstrate their clinical implications as diagnostic or prognostic biomarkers for CRC.

Key words: Long non-coding RNA; Colorectal cancer; Colorectal adenoma; Circulating long non-coding RNAs; Exosome; Biomarker; Diagnostic marker; Prognostic marker

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Core tip: The present review aims to shed light on the complex world of long non-coding RNAs (lncRNAs) by discussing their origin, localization, and functions. By summarizing the constantly growing body of knowledge about lncRNA expression in colorectal tissue and by focusing on potential circulating lncRNA markers, we aim to enhance the understanding of the comprehensive picture of their diagnostic and prognostic potential in precancerous colorectal adenomas and cancer.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most frequent malignant diseases worldwide with a remarkably high mortality rate^[1]. The number of CRC-related deaths can be reduced only by diagnosis at the earliest stage when the disease is more likely to be cured.

Long non-coding RNAs (lncRNAs), a novel family of non-protein coding RNAs (200 nt-10 kb) are of outstanding interest as their expression is often altered in various disease types including malignancies^[2]. They are known to have a crucial role in the regulation of gene expression, alternative splicing mechanisms, protein localization and activity, formation of cellular substructures and protein complexes through their diverse interactions with DNA, RNA and proteins^[3,4].

In cancers, lncRNAs are involved in every stage of carcinogenesis and tumor progression including tumor initiation, proliferation, apoptosis and migration of cancer cells, angiogenesis, tumor invasion and metastasis formation^[5,6]. Their altered expression can influence several oncogenic signaling cascades including the WNT/ β -catenin, PI3K/Akt, EGFR, NOTCH, mTOR and TP53 signaling pathways^[4,7-20]. Besides local expression changes in cancerous tissue and tumor-related stroma, lncRNAs also remain stable in body fluids due to their resistance to RNases^[2,21].

Several lncRNAs showing altered expression in colorectal tumors including precancerous adenomas have potential as early diagnostic markers^[22-24]. In this review, we summarize the colorectal tumor-related tissue and circulating lncRNAs, altered lncRNA expression patterns, and technical aspects of their isolation and detection. Our aim is to show their potential as diagnostic and prognostic biomarkers based on recently published data.

HISTORY, CLASSIFICATION, FUNCTION, LIFETIME AND SUBCELLULAR LOCALIZATION OF LNCRNAs

Regulatory non-coding RNAs (ncRNAs) were first reported in eukaryotes in the 1980s, of which H19^[25] and Xist^[26] were the first members of the family^[27]. When the Human Genome Project was completed, it became clear that only a minor part of our genome codes proteins and the rest was considered as "junk" DNA^[28]. Since then, our knowledge about the non-coding genome was expanded, and the still unexplored regulatory role of the ncRNA world is the focus of several studies and holds a significant clinical potential^[29]. Over the past decades, along with the development of explorative molecular biology methods, the importance and function of the complex eukaryotic transcriptome have been recognized, a large proportion of which comprises the actively transcribed lncRNAs^[30]. After the discovery and the intensive analysis of the class of small ncRNAs called miRNAs since 1993^[31], it became evident, that other ncRNAs also play fundamental role in gene expression regulation, and that their alterations can be responsible for the disrupted molecular pathways in multiple cancers^[32].

The major class of ncRNAs are lncRNAs, which are derived from highly diverse genomic context and are classified on the basis of the genomic region of origin^[28]. According to the genomic database [Ensembl Release 96 (April 2019)], human lncRNAs are categorized into 3prime overlapping ncRNA, antisense, lincRNA (long

interspersed ncRNA), retained intron, sense intronic, sense overlapping and macro lncRNAs. The lncRNAs that are not overlapping with protein-coding genes are called stand-alone lncRNAs including the large intergenic (or intervening) lncRNA (lincRNA) group^[28,33] (e.g., XIST, H19, MALAT1, and HOTAIR). Antisense lncRNAs are transcripts overlapping the genomic strand of a protein-coding locus in an antisense direction^[34], while sense lncRNAs are overlapped with the sense strand of protein coding genes containing exons^[35]. Antisense transcription is widespread in the mammalian genome^[36]; the estimated ratio of the genes with antisense transcripts varies from less than 2 to more than 70% of the total genes^[37]. XIST/TSIX is a well-known example of the sense-antisense transcript pairs^[38]. Pseudogenes are defined as nonfunctional sequences of genomic DNA originally derived from functional genes^[39]. Long intronic ncRNAs are transcribed from the intronic sequence of a coding gene. On the basis of their association with functional DNA elements, enhancer- and promoter-associated lncRNAs can be distinguished^[40]. The lncRNAs localize in the cytoplasm, nucleus, nucleolus, and also in other subcellular compartments and vesicles (such as nuclear bodies, exosomes) and the localization is related to their molecular functions^[41]. Certain sequence motifs in their primary sequence are associated with the subcellular localization^[42].

As the largest class of non-coding transcripts, lncRNAs have a wide variety of functions. They can act as RNAs (e.g., ribozymes, riboswitches)^[43] and widely as ribonucleoprotein particles (RNP)^[44]. They can exert their positive or negative regulating functions either *in cis* or *in trans*^[45]. One of their functions is the regulation of nuclear organization; lncRNAs can modulate the chromatin architecture (e.g., Xist) and they can also regulate inter- and intrachromosomal interactions (e.g., colorectal cancer associated transcript 1. long isoform (CCAT1-L) modulating interchromatin loops between enhancers and promoters^[46]). lncRNAs can regulate other non-coding RNAs (e.g., as miRNA sponges leading to reduced miRNA inhibitory effect on target molecules^[47]), and also can be processed into single- or double-stranded siRNAs^[3]. Several gene transcription processes can be activated or blocked by lncRNAs by recruiting or inhibiting transcription factors of the target gene promoters^[3,44]. Certain lncRNAs are linked to the process of alternative splicing (e.g., LINC001133)^[48]. Furthermore, protein activity is regulated by lncRNAs and trafficking between the subcellular compartments can also be influenced by lncRNAs^[49].

Nuclear lncRNAs also contribute to chromatin remodeling as they can promote or prevent the recruitment of chromatin modifiers^[46]. They are also part of nuclear bodies^[50] with scaffold function, so-called architectural lncRNAs^[51] [such as nuclear enriched abundant transcript 1 (NEAT1), as a well-characterized lncRNA as a crucial component of paraspeckles^[52]] and also as non-architectural lncRNAs [e.g., metastasis associated lung carcinoma transcript 1 (MALAT1) as one of the most abundant lncRNA in nuclear speckles^[46]].

Epigenetic mechanisms, such as histone modifications are also influenced by lncRNAs. For instance, lncRNA HOTAIR (homeobox transcript antisense intergenic RNA) interacts with both LSD1/CoREST/REST complex and PRC2 as a modular scaffold that leads to coupled histone H3 lysine 27 methylation and lysine 4 demethylation^[53].

By the modulation of all three major mammalian DNA methyltransferases (DNMT1, DNMT3a, DNMT3b), lncRNAs influence DNA methylation levels resulting in altered expression of the target genes^[44]. DNMT1-associated Colon Cancer Repressed lncRNA 1 (DACOR1) interacts with both chromatin and DNMT1 and targets DNMT1 protein complex to certain genomic loci, also affecting cellular SAM levels^[54,55]. Altogether, the expression alterations of lncRNAs influence many biological functions that contribute to the disturbance of the complex fine-tuning machinery of non-coding RNA regulatory network during cancer formation.

Our knowledge about the posttranscriptional regulation of lncRNAs is limited, however, the stability of transcripts can be an important aspect in gene expression regulation^[56,57] as the half-life of ncRNAs correlates with their functional characteristics^[58]. Each lncRNA has a unique structure, and these transcripts are characterized by complex secondary and tertiary structures which is crucial to exert their functions^[59]. Although the stability of these non-coding transcripts was generally considered to be lower compared to mRNAs^[60] on the basis of a genome-wide lncRNA analysis by Clark *et al.*^[56], a wide variety in their stability can be observed which is consistent with their functional diversity. lncRNA stability is correlated with genomic location, subcellular localization, splicing, and GC percentage, while in contrast, expression levels are not correlated with stability^[56]. The half-life of lncRNAs ranges from < 30 min to > 48 h with median value at 3.5 h, and they can be classified as unstable and to highly stable lncRNAs - the latter represented at a lower percentage^[56]. According to Clark *et al.*, nuclear-enriched lncRNAs displayed significantly lower stability compared to those detected both in nucleus and cytoplasm^[56]. It is

important to note that lncRNAs with even lower stability have been shown to have fundamental role (*e.g.*, NEAT1 as scaffold lncRNA of paraspeckles, as dynamic nuclear subdomains^[61]), furthermore, the existence of highly stable lncRNAs illustrate the biomarker potential of this subclass of non-coding transcripts.

LNCRNA EXPRESSION ANALYSIS METHODS

Analysis of lncRNAs is technically challenging due to their relatively low expression level and their tissue-specific expression^[62], therefore, the following methods are optimized for studying lncRNAs with high sensitivity and resolution.

High-throughput sequencing serial analysis of gene expression (SAGE) is based on short cDNA sequences containing recognition sites for restriction enzymes at the transcripts' 3' end, and it was one of the first transcriptome analysis methods to study lncRNA expression^[63,64].

Among whole genome analyses, microarrays are widely used to analyse the RNA expression in a high-throughput manner from the 2000s, however, these systems are limited to studying the known RNAs. Furthermore, cross-hybridization and limited detection range due to background and saturation signals make these analyses more challenging^[65]. In parallel, the rapid development of next generation sequencing (NGS) systems revolutionized the experimental field, as RNA-Seq provides a cost-effective and rapid solution for whole transcriptome profiling with the potential to discover novel transcripts^[65]. The higher resolution and reproducibility of RNA-Seq compared to microarrays^[65] resulted in broad use of this approach. RNA-Seq supports the annotation of novel lncRNAs, RNA editing sites, and alternative splicing sites, as well^[62]. Cap analysis of gene expression (CAGE) is an NGS-based approach to map and quantify the expression of 5' capped RNAs^[66] and also to identify transcriptionally active promoter regions and Pol II-driven TSSs^[64].

The lncRNAs regulate and mediate interactions on different molecular levels and complex networks of these non-coding RNAs remain to be explored. RNA-binding protein immunoprecipitation (RIP) is used to study RNA-protein interactions, where the RNA of interest can be complexed with its interacting proteins, and this fraction can be selectively pulled down^[67]. The downstream analysis can be performed by combining with the previously discussed methods, including RIP-Chip and RIP-Seq^[68]. Native RIP is suitable for the exploration of strong and direct RNA-protein interactions, whereas the crosslinked immunoprecipitation method (CLIP) is used to study weak or indirect binding^[62]. Crosslinking is achieved by ultraviolet light (UV) followed by RNase treatment and stringent washes which increases the specificity of the interaction detection^[69]. In order to minimize the disadvantages of CLIP, modified methods, such as individual nucleotide resolution CLIP (iCLIP)^[70], and photoactivable ribonucleoside-enhanced CLIP (PAR-CLIP) are also available for the identification of the exact crosslinking sites with single nucleotide resolution^[62,69].

Other RNA pull-down methods, such as chromatin isolation by RNA purification (ChIRP)^[71], capture hybridization analysis of RNA targets (CHART)^[72] and RNA antisense purification (RAP)^[73] can be applied to study RNA-DNA interactions to shed light on lncRNAs' functions and identify trans-genomic interacting sites^[62]. During ChIRP experiments, a biotin-labeled antisense probe designed to the selected lncRNA is employed to explore its interacting chromosomal fragments^[71]. Different probe design criteria are applied in the case of CHART, as in contrast with ChIRP probes spanning the whole interesting lncRNA, the CHART method uses capture oligos specific for the accessible regions of the lncRNA candidate^[72]. The co-purified RNA, DNA or proteins potentially interacting with the selected lncRNA can be analysed with NGS, PCR or Western blotting^[62]. RAP can be performed with different crosslinking methods (*e.g.*, psoralens) along with the longer biotinylated probes (> 60 bp) to enhance the RNA-DNA hybrid stability^[73] and to reduce the signal-to-noise ratio^[64].

lncRNAs are known to exert their function also by binding directly or indirectly to other RNAs^[64]. These interactions can be studied by RAP-RNA (applying different chemical cross-linking), as 4' aminomethyltrioxalen: RAP-RNA^[AMT], formaldehyde: RAP-RNA^[FA], FA and disuccinimidyl glutarate: RAP-RNA^[FA-DSG]^[74] or UV-crosslinked CLASH (cross-linking, ligation and sequencing of hybrids)^[75] methods.

It is known that lncRNAs fold into secondary and tertiary structures that are crucial to exert their regulatory effects^[59], but the structural domains of the RNA interactome still need to be explored. Structural relationships can be studied by dimethyl sulfate sequencing (DMS-Seq), selective 2'-hydroxyl acylation analysed by primer extension sequencing (SHAPE-Seq), genome-wide fragmentation sequencing (FRAG-Seq), and parallel analysis of RNA structure (PARS) techniques^[76]. By the intensive development

of subcellular visualization approaches, lncRNAs can be localized within the cell with high sensitivity using special fluorescent *in situ* hybridization (FISH) applications (single molecule FISH - smFISH, sequential FISH - seqFISH, and multiplexed error-robust FISH - MerFISH)^[77-79]. High resolution microscopes, as structured illumination microscopy (SIM)^[80] or stochastic optical reconstruction microscopy (STORM)^[81] enable the precise detection of certain lncRNAs and investigation of their colocalization partners^[46]. The functional investigations of lncRNAs can be performed with antisense oligonucleotides (ASO) and also by siRNAs and shRNAs *via* binding and affecting the target lncRNA's functionality^[82]. The CRISPR-Cas9 genome editing technique^[83] has revolutionized functional studies in the lncRNA world, which can be employed to silence (CRISPRi^[84]) and also to overexpress (CRISPRa^[85]) the lncRNA of interest^[86].

LNCRNA EXPRESSION ALTERATIONS IN COLORECTAL ADENOMA AND CANCER TISSUE

Increasing evidence suggest that lncRNAs are involved in the whole process of CRC development, progression and metastasis formation - similarly to their diverse regulatory role in other types of malignancies - affecting the essential signaling pathways including WNT, TP53, PI3K/Akt, mTOR, EGFR and NOTCH1 in CRC^[4-20]. Abnormal expression of numerous lncRNAs including the well-known HOTAIR^[87-90], MALAT1^[91-93] and H19^[94,95] has been described in CRC compared to normal colonic tissue samples (Table 1). From a clinical point of view, lncRNAs - with altered expression in different stages of colorectal carcinogenesis, and disease progression - have a particularly great potential to become early diagnostic and/or prognostic biomarkers.

Several studies reported the altered expression of certain lncRNAs including colon cancer associated transcript-1 (CCAT1), colorectal neoplasia differentially expressed (CRNDE-L), colorectal cancer associated lncRNA (CRCAL) 1, -2, -3 and -4 and urothelial carcinoma-associated 1 (UCA1) already in precancerous adenomas^[23,24,37,96-102].

Nissan *et al*^[96] in their comprehensive RT-qPCR study were the first to demonstrate the massive (often more than 100-fold) upregulation of CCAT1 in CRC and premalignant adenoma tissue samples compared to normal colonic mucosa. Furthermore, elevated CCAT1 levels could be detected in lymph node and distant liver metastases, as well as in peripheral blood mononuclear cells (PBMCs) of CRC patients^[96]. Alaiyan *et al*^[23] have confirmed the overexpression of CCAT1 in precancerous conditions and through all CRC stages using RT-qPCR and *in situ* hybridization (ISH). These data suggest its essential role in both early carcinogenesis and metastatic processes, moreover, *in vitro* studies revealed that the c-Myc oncogene could facilitate the transcription of CCAT1 by binding to its promoter^[97]. CRNDE also becomes activated already in the initial steps of tumor development as its elevated expression was observed in > 90% of neoplastic colon tissue including adenoma and adenocarcinoma samples using both microarray and RT-PCR technology^[24]. Liu *et al*^[103] found significant upregulation of CRNDE-h splice variant both in adenoma and CRC tissues compared to control groups containing normal adjacent, inflammatory bowel disease and hyperplastic polyp samples. Moreover, within the CRC group, increased expression of CRNDE-h showed significant correlation with tumor size, lymph node, and distant metastasis. It was observed in *in vitro* studies, that lncRNA CRNDE can promote CRC development and progression through epigenetic silencing of dual-specificity phosphatase 5 (DUSP5) and cyclin-dependent kinase inhibitor 1A (CDKN1A)^[104] or *via* activating Ras/MAPK^[105] and WNT/ β -catenin^[106,107] signaling pathways. Furthermore, it can contribute to chemoresistance by sponging microRNAs (miR-136^[108], miR-181a-5p^[107]) in CRC.

Some colorectal cancer associated lncRNAs [CRCALs: CRCAL-1 (AC021218.2), CRCAL-2 (LINC00858), CRCAL-3 (RP11-138J23.1) and CRCAL-4 (RP11-435O5.2)] were identified as overexpressed and novel CRC biomarkers using RNA-sequencing techniques^[100]. These lncRNAs may "be involved in the very early steps of the neoplastic process" as the expression levels of all four CRCALs were found to be elevated in colorectal adenoma samples, as well. RNA interference-mediated knockdown experiments and gene ontology analysis of The Cancer Genome Atlas (TCGA) dataset suggest the involvement of CRCAL-3 and CRCAL-4 in cell cycle regulation^[100].

Several studies have also indicated the tumor-promoting role of UCA1 lncRNA in CRC^[101,102,109]. Intensive UCA1 expression was found to be correlated with larger tumor size, depth of invasion, and a less differentiated histology^[110]. Moreover, elevated

Table 1 Tissue and circulating long non-coding RNAs with altered expression in colorectal cancer

lncRNA	Tissue	Plasma/serum	Exosome	Expression in CRC	Ref.	Potentially diagnostic marker	Prognostic role
91H	X	X	X	Up	[130,138,152]	X (comb 1)	Up - poor prognosis
ADAMTS9-AS2	X			Down	[145]		Down - poor prognosis
AFAP1-AS1	X			Up	[145,153,154]		Up - poor prognosis
AK027294	X			Up	[155]		
AK123657/BX64 820	X			Down	[156]		Down - poor prognosis
AK307796	X			Up	[157]		
ANRIL	X			Up	[158,159]		Up - poor prognosis
ATB	X	X		Up	[122,160,161]		Up - poor prognosis
BA318C17.1	X			Down	[162]		
BANCR	X	X		Down/up	[125,163,164]	X (comb 2)	Prognostic
BCAR4/HOXA-AS2	X	X	X	Up/down	[140,145]	X	Up - poor prognosis
BLACAT1	X	X		Up	[129,151,165]		Up - poor prognosis
CAHM	X			Down	[131]	X	
CASC11	X			Up	[166]		
CASC2	X			Down	[167]		Down - poor prognosis
CCAL	X			Up	[4]		Up - poor prognosis
CCAT1	X	X		Up	[23,96-98,116,168-170]	X	Up - poor prognosis
CCAT1-L	X			Up	[171]		
CCAT2	X	X		Up	[134,172,173]	X	Prognostic
CLMAT3	X			Up	[174,175]		Up - poor prognosis
CRNDE	X	X	X	Up	[24,99,103]	X	Up - poor prognosis
CRCAL-1/AC021218.2	X			Up	[100]	X	
CRCAL-2/LINC00858	X			Up	[100]	X	
CRCAL-3/RP11-138J23.1	X			Up	[100]	X	
CRCAL-4/RP11-453O5.2	X			Up	[100]	X	
CTD903	X			Down	[176]		Down - poor prognosis
CTNNAP1	X			Down	[177]	X	
DACOR1	X			Up	[54]		
DANCR	X			Up	[178]		Up - poor prognosis
DQ786243	X			Up	[179]		Prognostic
E2F4 antisense	X			Up	[180]		
ENST00000430471	X			Up	[181]		
ENST00000455974/AC123023.1	X			Up	[111]	X	Up - poor prognosis
ENST00000465846	X			Down	[157]		
FER1L4	X	X		Down	[123]		Down - poor prognosis

FEZF1-AS1	X			Up	[115,182]		Up - poor prognosis
FTX	X			Up	[183]		Up - poor prognosis
GAPLINC	X			Up	[184]		Prognostic
GAS5	X	X	X	Down	[120,185-188]		Down - poor prognosis
GKET1	X			Up	[189]		
lnc-GNAT1-1		X			[119]		
H19	X			Up	[94,143-145,190,191]		Up - poor prognosis
HIF1-AS1	X	X			[132]		Up - poor prognosis
HIF2PUT	X			Up	[192]		
HOTAIR	X	X		Up	[87-90,116,193,194]		Up - poor prognosis
HOTAIRM1	X	X		Down	[117]		Down - poor prognosis
HOTTIP	X			Up	[195,196]		Up - poor prognosis
HULC	X	X		Up	[134,197]		Up - poor prognosis
KCNQ1OT1	X			Up	[198,199]		
LINC00152 (CYTOR)	X			Up	[8,11,13]		Up - poor prognosis
LINC01133	X			Down	[200]		Down - poor prognosis
LINC01296	X			Down	[201]		Down - poor prognosis
lincRNA-p21	X	X		Down	[116,202-204]		Down - poor prognosis
Lnc34a	X			Up	[205]		
lncRNA-LET/ NPNT-IT1	X			Down	[206]		
LNCV6_116109			X	Up	[139]	X	
LNCV6_98390			X	Up	[139]	X	
LNCV6_38772			X	Up	[139]	X	
LNCV6_108226			X	Up	[139]	X	
LNCV6_84003			X	Up	[139]	X	
LNCV6_98602			X	Up	[139]	X	
LOC152578		X		Up	[126]	X (comb 3)	
LOC100287225	X			Down	[207,208]		
LOC285194/TU SC7	X	X		Down/Up	[124,209,210]	X (comb 4)	Down - poor prognosis
Loc554202	X			Down	[211,212]		Down - poor prognosis
MALAT1	X	X		Up	[7,91-93,145,149,213,214]		Up - poor prognosis
MEG3	X	X		Down	[100,130,215-218]	X (comb 1)	Down - poor prognosis
Nbla12061		X		Up	[124]	X (comb 4)	
ncNRFR	X			Up	[219]		
ncRAN	X			Down	[220,221]		Down - poor prognosis
ncRuPAR	X			Down	[222]		Down - poor prognosis
NEAT1	X	X		Up	[128,223]		Up - poor prognosis
NORAD		X			[133]		
NR_026817		X		Down	[125]	X (comb 2)	Prognostic
NR_029373	X	X		Down	[125]	X (comb 2)	Down - poor prognosis

NR_034119		X		Down	[125]	X (comb 2)	
PANDAR	X			Up	[224]		Up - poor prognosis
PCAT-1	X			Up	[225]		Up - poor prognosis
PRNCR1	X			Up	[226,227]		
PVT-1	X	X		Up	[130,145,228]	X (comb 1)	Up - poor prognosis
RP1-13P20.6	X			Down	[229]		Down - poor prognosis
RP11-462C24.1	X	X		Down/Up	[124,230,231]	X (comb 4)	Down - poor prognosis
SLC25A25-AS1	X	X		Down	[118]		Down - poor prognosis
SnaR	X				[232]		
SNHG20	X			Up	[233]		Prognostic
SNHG12	X			Up	[234]		Up - poor prognosis
Sox2ot	X			Up	[235]		
SPRY4-IT1	X	X		Up	[121,236]		Up - poor prognosis
TINCR	X			Down	[100,237]		
TUG1	X	X	X	Up	[101,238-240]		Up - poor prognosis
uc.388	X			Down/Up	[241,242]	X	Prognostic
uc.73a	X			Down/Up	[241,242]	X	
uc002kmd.1	X			Up	[243]		
UCA1	X	X	X	Up	[100,101,110,244,245]		Up - poor prognosis
UPAT	X			Up	[246]		
XIST	X	X		Up	[247,248]		Prognostic
XLOC_000303		X		Up	[136]	X (comb 3)	
XLOC_006844	X	X		Up	[136]	X (comb 3)	
ZFAS1	X	X		Up	[19,249]		Up - poor prognosis
ZNF582-AS1	X			Down	[250]	X	

The altered expression of long non-coding RNAs in colorectal cancer tissue, plasma/serum or exosomes and the potential diagnostic value are marked with X, respectively. Combined marker sets are also represented (comb 1, comb 2, comb 3 and comb 4).

UCA1 levels could be detected in precancerous adenomas which increase in CRC^[102].

In a recent publication, Lao *et al.* have described the gradual elevation of expression of a novel lncRNA, AC123023.1-201 (ENST0000455974) along the colonic normal-adenoma-dysplasia-carcinoma-metastasis sequence^[111]. High levels of this lncRNA were found to be significantly associated with poor survival of DNA mismatch repair proficient (pMMR) CRC patients. *In vitro* studies suggest that AC123023.1-201 might exert an oncogenic role in the pathomechanism of pMMR CRC *via* promoting JAG2-mediated Notch signaling^[111].

LNCRNA MARKERS IN PLASMA/SERUM OF COLORECTAL TUMOR PATIENTS AND THEIR MALIGNANCY-RELATED CELL FUNCTIONS

lncRNA molecules can cross the cell membrane, and hence can be found in different body fluids, such as blood, plasma/serum or urine^[112]. They can be derived from apoptotic and necrotic cells, or from living cells by an active manner. These molecules occur in association with RNA-binding proteins or lipoprotein complexes, however, extracellular vesicles are reported to be the primary source of plasma lncRNAs^[113]. These forms contribute to the relative resistance to degradation by RNase enzymes that make circulating lncRNAs promising markers for the prognosis, diagnosis, or screening of various diseases, including CRC^[114]. The altered expression levels of

several lncRNAs were reported in tumor tissues of CRC patients, and recently, additional articles have been published describing their presence in plasma or serum samples^[115]. CCAT1 and HOTAIR are among the first markers reported to have significantly elevated expression in the plasma of CRC patients compared to healthy controls^[116]. It was also observed that after surgical treatment of CRC patients, the serum levels of these lncRNAs decreased in comparison with pre-operative samples. HOTAIR expression was also reported in peripheral blood mononuclear cells (PBMC) of CRC blood donors as compared with controls; of note, patients with right-sided CRC had lower levels of HOTAIR lncRNA than those with left-sided cancers^[90]. In contrast, HOX antisense intergenic RNA myeloid 1 (HOTAIRM1) showed reduced expression in tumor tissue, and low levels were reported in plasma of CRC patients compared to healthy controls using nested TaqMan RT-PCR method^[117]. It has been assumed that this lncRNA can inhibit intense cell division and therefore, it may function as a tumor suppressor. The expression of lncRNA SLC25A25-AS1 was also significantly decreased in both tumor tissue and serum samples, and based on *in vitro* measurements, it was observed that downregulation of SLC25A25-AS1 has an impact on chemoresistance and induces the epithelial-mesenchymal transition (EMT) process^[118]. Low levels of lnc-GNAT1-1 were detected in the plasma of CRC patients, and with advanced TNM stages, the level of this lncRNA decreased in the peripheral blood^[119]. lncRNA growth arrest specific transcript 5 (GAS5) had diminished expression in serum samples of 109 CRC patients compared with 99 healthy controls^[120]. Further experiments highlighted that low level of GAS5 was correlated with advanced TNM stages and larger tumor size. lncRNAs that can enhance cell proliferation were also described in some reports. For instance, lncRNA SPRY4-IT1 was found to be significantly upregulated in CRC tissue and serum samples, and its increased expression was associated with late TNM stages. It influences proliferation, migration, and invasion of CRC cells, and has an effect on the expression of EMT-related genes^[121]. Long non-coding RNA-activated by TGF- β (lncRNA-ATB) has been analysed in 50 preoperative and postoperative plasma samples of cancer patients and in 50 healthy volunteers, and its overexpression was reported in 70% (35/50) of CRC cases one month after surgery^[122]. Moreover, lncRNA-ATB levels were found to be significantly higher in postoperative plasma in comparison with preoperative samples, suggesting that lncRNA might be released by other mechanisms than by the primary tumor. This research group described another lncRNA, fer-1-like protein 4 (FER1L4) that showed decreased expression level in postoperative blood samples compared with the matched preoperative ones in contrast to the above-mentioned lncRNA-ATB^[123]. Wang *et al.* compiled a panel of lncRNA containing 3 RNAs (LOC285194, RP11-462C24.1, and Nbla12061) that were upregulated in 61 CRC serum samples compared to healthy controls ($n = 60$)^[124]. Another study selected four lncRNAs (BANCR, NR_026817, NR_029373, and NR_034119) for further experiments after high-throughput microarray analysis, and concluded that this panel was dysregulated in tissue and serum samples of colon carcinoma patients^[125]. Shi *et al.*^[126] also performed microarray analysis on the circulating plasma lncRNA fraction using Human lncRNA Array v3.0, and 8 transcripts were further examined with RT-qPCR technique. From these candidates, expression of three (XLOC_006844, LOC152578, and XLOC_000303) lncRNAs were found to be significantly higher in CRC plasma samples ($n = 220$) compared to cancer-free controls ($n = 180$). Another lncRNA, nuclear-enriched abundant transcript 1 (NEAT1) was identified based on microarray results as the most significantly upregulated gene in whole blood samples of CRC patients^[127]. Two variants of this lncRNA, NEAT1_v1 and NEAT1_v2 were studied separately, and high levels of both two transcripts were observed^[128]. Moreover, Wu *et al.*^[129] showed that knockdown of NEAT1_v1 caused inhibition of cell invasion and proliferation *in vitro*, while in case of NEAT1_v2, the knockdown of the transcript could induce cell growth. Similarly to the previous studies, lncRNA bladder cancer associated transcript 1 (BLACAT1) was also found to be overexpressed using microarray analysis and the increased expression was confirmed using RT-PCR in CRC serum samples. Liu *et al.* selected 3 lncRNAs, H19 antisense (91H), plasmodioma variant translocation 1 (PVT-1) and maternally expressed gene 3 (MEG3) and reported increased levels in plasma of CRC patients compared to non-cancerous controls^[130]. Our knowledge on the regulation of lncRNA gene expression is incomplete; however, a study by Pedersen *et al.*^[131] demonstrated reduced level of lncRNA CAHM in CRC patients coupled with elevated methylation of CAHM gene, which was detectable also in plasma samples.

Additional circulating lncRNAs have been described as potential biomarkers for CRC detection (*e.g.*, HIF1A-AS1, NORAD, CCAT2 or HULC), and more are expected to be identified in the near future^[132-134]. The most promising lncRNAs to date are summarised in Table 1.

APPEARANCE OF LONG NON-CODING RNAS IN EXOSOMES

Exosomes are a subgroup of extracellular vesicles (EVs) that can be found in different body fluids, including blood, serum/plasma, urine or saliva. The particles range from 30 to 100 nm in diameter, and around 2×10^{15} exosomes have been identified in the blood of healthy people; however, in case of cancer, the exosome numbers can increase, and reaching 4×10^{15} ^[135,136]. Recent studies highlighted that exosomes secreted by tumor cells contain DNAs, proteins, lipids, different small molecules and RNAs including lncRNAs, and these molecules may also be taken by target cells. Therefore, the contents of exosomes can influence the biological functions of the recipient cells and play an important part in long distance cell-cell communication^[137].

Several differentially expressed lncRNAs in exosomes were reported in plasma/serum samples of CRC patients. According to Liu *et al.*^[103], colorectal neoplasia differentially expressed-h (CRNDE-h) showed elevated expression in isolated exosomes of 148 CRC patients compared to benign colorectal disease patients and healthy controls. Moreover, it was observed that a high exosomal level of this lncRNA correlated with both lymph node and distant metastasis and was related to low overall survival rates. Expression of exosomal lncRNA 91H also increased in CRC serum samples, which occurs at a higher level in the vesicles, than in exosome-free sera^[138]. It has been also reported that the elevated expression was decreased after surgery. Based on real-time PCR results, Barbagallo *et al.*^[101] demonstrated that UCA1 in serum exosomes of cancerous patients was downregulated, while taurine up-regulated 1 (TUG1) was overexpressed. Another study constructed a six-member (LNCV6_116109, LNCV6_98390, LNCV6_38772, LNCV_108266, LNCV6_84003 and LNCV6_98602) panel of plasma exosomal lncRNAs based on microarray analysis that indicated overexpression in CRC patients compared to healthy individuals^[139]. The increased level was already observed in the early stages of CRC suggesting that these lncRNAs are potential markers for early detection of cancer. Dong *et al.*^[140] showed that two mRNAs (KRTAP5-4 and MAGEA3) and one lncRNA (BCAR4) extracted from sera exosomes are present at a lower level in colorectal adenoma and carcinoma patients compared to healthy individuals, and the combination of these RNAs could be used as CRC biomarkers. Interestingly, according to Li *et al.*^[120] lncRNA GAS5 was found to be downregulated in CRC sera samples and acts as a tumor suppressor in cancer development, however, another study revealed that this lncRNA was upregulated in tissues, plasma and exosomes of CRC patients and its expression was related to TNM stage, Dukes stage, lymph node metastasis, local recurrence rate and distant metastasis rate^[141].

Analysis of lncRNAs in exosomes is ongoing, and because altered levels of lncRNAs can serve as a potential markers for CRC detection, clarification of their function in cancer development is also a crucial step. The exosomal lncRNAs with altered expression in CRC are listed in Table 1.

CLINICAL RELEVANCE OF ALTERED LONG NON-CODING RNA EXPRESSION PATTERNS IN CRC

Biomarkers - as objectively measurable molecules suitable for monitoring physiological and pathological processes and the effect of treatments - have a crucial role in the clinical workup of tumors, enhancing the early diagnosis, classification of tumors, monitoring therapy response, and supporting the evolvement of personalized therapies, as well^[21]. lncRNAs can serve as diagnostic, prognostic and predictive biomarkers in malignant diseases including CRC^[22]. Principally, lncRNAs with altered levels in different stages of tumorigenesis and progression have a great potential to become early diagnostic and/or prognostic biomarkers. Besides the remarkable expression difference associated with disease stages, the important aspect of their presence and stability in the circulatory system are opening a new path for noninvasive diagnostic applications^[21,142]. CCAT1 can serve as a promising marker for early CRC recognition due to its high expression in malignant and benign colorectal tumors compared to normal controls^[23,96], and its detection both in PBMC and plasma samples, as well^[96,116]. Increased plasma CCAT1 could predict the presence of CRC with 75.7% sensitivity and 85.3% specificity^[116]. Almost all splice variants of CRNDE lncRNA, (except for CRNDE-d), and particularly CRDNME-b and CRNDE-h, were found to be intensively (approximately 5- to 100-fold) upregulated in both benign and malignant neoplastic colorectal tissue^[24]. On the basis of CRNDE-h expression levels, CRC and normal tissue samples could be discriminated with 85% sensitivity and 96% specificity, which was also proven to be a highly sensitive and specific marker in

adenoma *vs* normal tissue comparison (sensitivity: 95%, specificity: 96%)^[24]. Based on CRNDE-h levels in tissue, CRC could be differentiated from adenoma and healthy tissues with 70.4% sensitivity and 70.8% specificity^[99]. Its strong diagnostic potential was also supported by the circulating CRNDE-h RT-qPCR results at a reported 87% sensitivity and 93% specificity between CRC *vs* healthy controls^[24]. Moreover, the analysis of exosomal CRC-related CRNDE-h of serum also allowed separation of CRC samples from benign and healthy controls (AUC = 0.892, sensitivity: 70.3%, specificity: 94.4%)^[103]. The newly identified upregulated CRCAL1-4 lncRNAs might be suitable for early recognition of colorectal neoplasias, however, only marginal significance could be observed between adenoma and CRC^[100]. Potential utilization in CRC screening and diagnostics of several other differentially expressed lncRNAs including BLACAT1^[129], CCAT2^[134], HULC^[134], NEAT1^[128], UCA1^[101,109] and HOTAIRM1^[117] has also emerged in RT-qPCR studies analyzing circulating lncRNAs resulting in various specificity (43%-96%) and sensitivity (55%-100%) values. In addition to the altered expression levels, the DNA methylation changes of lncRNAs can hold a discriminative ability, as the amount of methylated CAHM DNA molecules in the circulatory system depends on the CRC stages; hence it can serve as a promising marker for CRC screening^[131].

In addition to single lncRNA marker candidates, lncRNA marker combinations and multi-marker lncRNA panels have also been identified as a potential diagnostic approach. By testing the CRC diagnostic efficacy of circulating HOTAIR and CCAT1, the combined measurement of their plasma/serum levels resulted in higher sensitivity and specificity values (84.3% and 80.2%, respectively) than the above-mentioned markers alone^[116]. This marker combination could provide an effective CRC diagnosis performance, moreover, it could detect CRC efficiently already at an early stage (85%). Analysis of Barbagallo *et al*^[101] revealed that diagnostic accuracy of serum exosome UCA1 levels for CRC (sensitivity: 100%, specificity: 43%) could be enhanced by applying it in combination with TUG1 lncRNA (sensitivity: 93%, specificity: 64%) or with circHIPK3 circular non-coding RNA (sensitivity: 100%, specificity: 70%). A promising lncRNA panel containing three lncRNAs (LOC152578, XLOC_000303, and XLOC_0006844) upregulated in CRC was identified and validated on a large independent plasma sample cohort (220 CRCs, 180 controls) (positive predictive value: 0.80, negative predictive value: 0.84, AUC = 0.975)^[126]. The double-blind test on another 100 plasma samples (50 CRC, 50 cancer-free controls) also confirmed that the above-mentioned biomarker set is suitable for indicating the occurrence of CRC with 85% accuracy^[126]. CRC and healthy normal cases could be distinguished based on the increased serum levels of LOC285194, RP11-46C24.1, and Nbla12061 lncRNAs (AUC = 0.793, sensitivity: 68.33%, specificity: 86.89%)^[124]. The predictive value of this lncRNA signature was significantly higher than of the conventional clinical serum protein markers (CEA, CA199, CA125, and CA724) (AUC values were 0.633, 0.567, 0.517 and 0.592, respectively)^[124]. Microarray analysis of CRC-NAT tissue sample pairs revealed a four-lncRNA panel (upregulated BANC1 and downregulated NR_026817, NR_029373, NR_034119) which had consistently altered pattern both in CRC tissue and serum samples compared to normal controls^[125]. The high AUC, specificity and sensitivity values for both the training and validation sample sets support the reliable diagnostic ability of this biomarker set (AUC: 0.891 and 0.881; specificity: 80% and 75.83%; sensitivity: 81.67% and 89.17%) which even exceeded the diagnostic power of CEA^[125]. A pilot study of Liu *et al.* revealed a new promising diagnostic plasma ncRNA biomarker set (H91, PVT-1, MEG3) for early-stage CRCs as the panel could differentiate CRC samples from controls with 82.76% sensitivity and 78.57% specificity^[130].

According to the lnc2Cancer 2.0 database (www.bio-bigdata.com/lnc2cancer), the most frequently described lncRNAs with prognostic value in CRC are H19^[95,143-145], CRNDE^[99,103,105,107,146], HOTAIR^[89,90,147,148] and MALAT1^[92,145,149] (Supplemental Table 1). *In silico* lncRNA expression analysis of CRC data from The Cancer Genome Atlas (TCGA) database ($n = 534$) showed that H19 was the lncRNA mostly associated with the overall survival (OS) of CRC patients ($P = 0.0005$), independently from tumor stages^[143]. Elevated H19 levels were found to be correlated with tumor differentiation and advanced TNM stage^[144], and its expression could be considered as an independent predictor for OS and disease-free survival (DFS). Other studies also confirmed that overexpression of H19 lncRNA could predict the unfavorable prognosis in CRC^[145]. CRNDE-h can serve as a promising early diagnostic biomarker for CRC, and it also has a prognostic capability due to its high tissue and serum exosome levels significantly correlated with tumor size, lymph node, and distant metastasis^[99,103]. In addition, increased exosomal CRNDE-h levels were proven to be a negative predictor of OS of CRC patients [34.6% (high CRNDE-h) *vs* 68.2% (low CRNDE-h), $P < 0.001$]^[103]. Similar associations with CRC stages were reported for CRNDE-p, another overexpressed transcript variant of CRNDE^[146]. HOTAIR lncRNA

was also observed to be a negative prognostic factor in CRC, as its upregulated expression in primary tumor tissue, even more in blood of CRC patients were found to be associated with higher mortality [Cox's proportional hazard, hazard ratio (HR) (tissue) = 4.4, HR (blood) = 5.9]^[90]. Significant differences in clinicopathological parameters such as less differentiated histology, greater tumor depth, and liver metastasis were observed in CRC cases with high HOTAIR expression ($n = 20$) compared CRCs with low HOTAIR levels ($n = 80$) ($P < 0.05$)^[89]. Results of several other studies verified the correlation of higher HOTAIR levels with poorer OS^[89,148]. With the RT-qPCR analysis of tissue samples from 146 stage II/III CRC patients, it was observed that patients with more intense MALAT1 lncRNA expression had a significantly worse prognosis with a HR of 2.863 for DFS and 3.968 for OS^[92]. Moreover, high MALAT1 levels were found to be associated with decreased patient survival and poor response to oxaliplatin-based chemotherapy in advanced CRC patients suggesting its utility as a prognostic marker and therapeutic target in CRC^[149].

In addition to CRNDE^[103,146] and HOTAIR^[90,116], among the 31 potentially prognostic lncRNAs published in at least two independent studies, CCAT2^[150], GAS5^[141], BLACAT1^[129], CCAT1^[96,116], NEAT1^[128], 91H^[138] and BANC1^[125] lncRNAs were also detectable in the circulation suggesting their application as minimally invasive markers for CRC prognosis (Table 1 and Supplemental Table 1). As reported by Ozawa *et al.*^[150] in a study involving two independent cohorts, the evaluation of CCAT2 expression in combination with CCAT1 may be a powerful tool for predicting tumor recurrence and prognosis in CRC patients. According to the expression analysis in tissue, plasma and exosome samples, GAS5 had a prognostic value in CRC based on its expression that was negatively correlated with TNM status, Dukes stage, and lymph node metastasis (LNM), local recurrence and distant metastasis rate, while its level was in positive relation with differentiation degree and the 3-year OS rate^[141]. On the other hand, elevated BLACAT1 expression could be considered as an independent unfavorable prognostic indicator for CRC, as it was observed to be associated with advanced CRC stages and shorter OS^[151]. The predictive potential of lncRNA transcript variants can differ, as the OS of CRC patients with intensive NEAT1_v1 expression was worse, while high levels of the other isoform, NEAT1_v2 was correlated with better OS^[128]. Determination of clinical significance of elevated exosomal H91 lncRNA expression suggested that it might be an early minimal invasive biomarker for CRC recurrence or metastasis^[138]. Gong *et al.*^[132] evaluated the diagnostic and prognostic value of increased serum HIF1A-AS1 levels in 151 CRC and 160 healthy control samples by RT-PCR, and reported a high diagnostic efficacy (86.8% sensitivity and 92.5% specificity); moreover, it was described as a predictor for worse prognosis in CRC.

In addition to the diagnostic and prognostic utility of lncRNAs with altered expression, ongoing research focused on the role of lncRNAs in chemoresistance and therapy response prediction are revealing several lncRNAs which could be promising therapeutic targets in CRC. Similarly to the above-mentioned MALAT1 whose increased levels were found to be associated with poor response to oxaliplatin (OXA)-based chemotherapy^[149], CRNDE can also contribute to oxaliplatin resistance in CRC^[107,108]. According to a recent *in vitro* study, CRNDE facilitates the resistance against OXA or 5-fluorouracil (5FU) treatment *via* miR-181a-5p-mediated regulation of Wnt/ β -catenin signaling^[107]. Association between high HOTAIR expression and poor response to 5FU treatment was assessed^[147]. HOTAIR can contribute to 5FU resistance through suppressing miR-218 and activating NF- κ B signaling in CRC^[147]. HOTAIR was observed to be upregulated in drug-resistant cisplatin- or paclitaxel-treated SW620 and Colo205 CRC cells, as well^[148] and could affect the chemoresistance of CRC *via* miR-203a-3p-mediated modulation of Wnt/ β -Catenin pathway^[148]. The most important tissue and circulating lncRNAs with diagnostic and prognostic potential in colorectal tumors are represented in Figure 1.

CONCLUSION

The increasing number of genome-wide expression analysis studies have led to the identification of a number of long non-coding RNAs with altered expression patterns in cancers including CRC. lncRNAs are proven to contribute to each step of the colorectal carcinogenesis and tumor progression by influencing the key cancer-related signal transduction pathways such as WNT/ β -catenin, PI3K/Akt, EGFR, NOTCH, mTOR and TP53 signaling. Dysregulated lncRNAs can appear in the pre-malignant adenoma stage of CRC and the expression alterations of a relatively large number of lncRNAs were found to be associated with clinicopathological parameters indicating CRC progression. Furthermore, lncRNAs are stable and detectable in body fluids

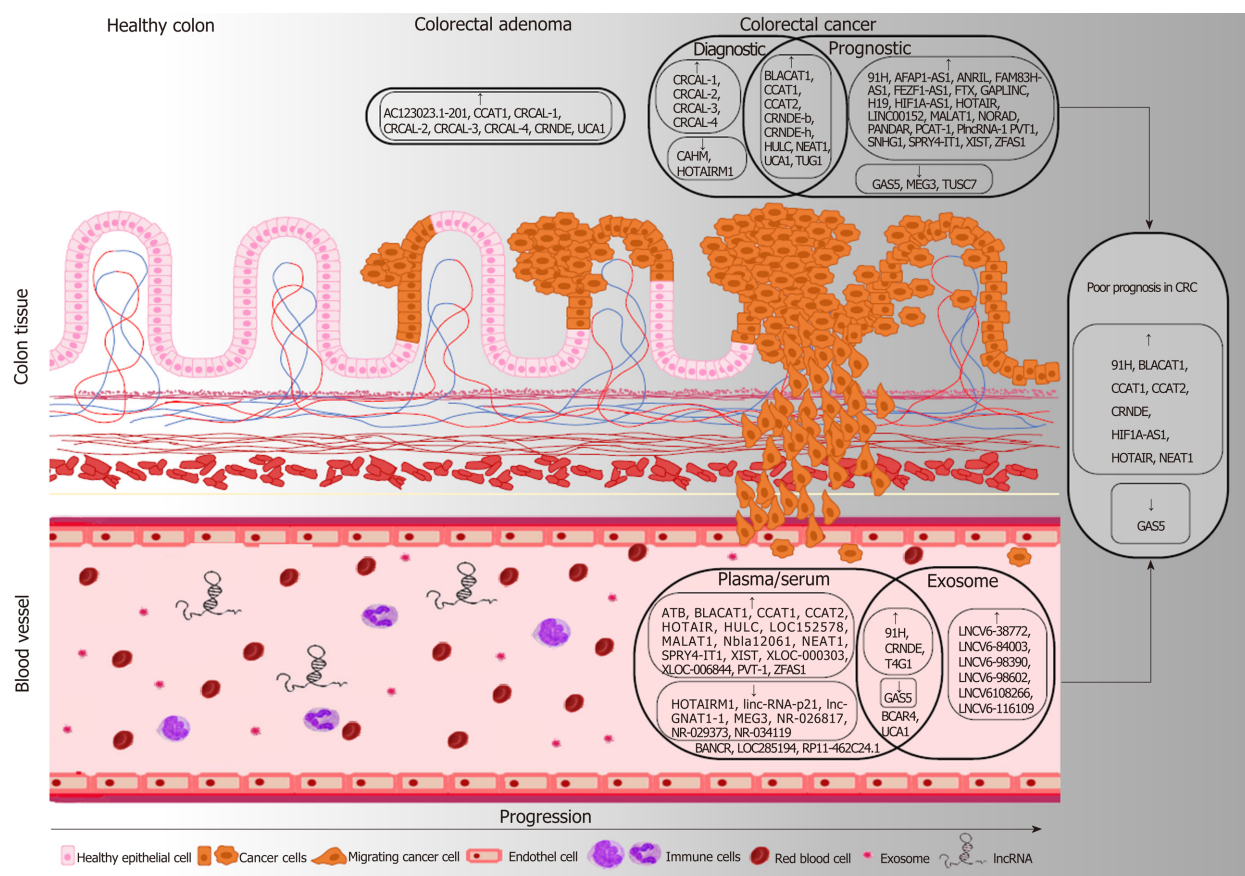


Figure 1 The most important tissue and circulating long non-coding RNA candidates with diagnostic and prognostic potential in colorectal tumors. Long non-coding RNA (lncRNAs) upregulated in adenoma or colorectal cancer (CRC) samples compared to normal controls are marked with ↑, while the downregulated lncRNAs are depicted with ↓. Potential prognostic markers detectable both in tissue and blood specimens are highlighted in the right, where ↑ refers to lncRNAs whose higher levels were found to be associated with poor prognosis (CRNDE, HOTAIR, CCAT2, BLACAT1, CCAT1, NEAT1, 91H, HIF1A-AS1), while the low expression of lncRNA marked with ↓ (GAS5) can be a predictor of worse disease outcome in CRC patients. In case of the lncRNAs written without frame (BANCR, BCAR4, LOC285194, RP11-462C24.1, UCA1), diverse, sometimes controversial expression data are available in the scientific literature.

facilitating their utilization as early detection and prognostic biomarkers. In order to open the door for implementation of minimally invasive lncRNA-based tests in the clinical practice, certain relevant technical aspects should be considered: (1) Standardization of the pre-processing and sample preparation procedure including the applied blood collection tubes, sample storage conditions and time, optimized lncRNA isolation protocols from liquid biopsy samples; (2) Selection of appropriate quantification, quality checking and sensitive techniques allowing the precise detection of cancer-related alterations; and (3) Application of proper universal endogenous controls for increasing the reliability and the accuracy of RT-qPCR measurements. For the development of adequately sensitive and CRC-specific, clinically applicable diagnostic and prognostic tests based on lncRNA markers/marker panels, validation studies with large sample cohorts are essential. On the other hand, as recent studies shed light on the potential role of lncRNAs as novel therapeutic targets, the specific lncRNA expression alterations in liquid biopsy samples may contribute to the improved early recognition, prognosis prediction and therapy monitoring in CRC. Moreover, lncRNAs as druggable targets might represent the basis of novel therapeutic methods in the fight against cancer.

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REFERENCES

- 1 **Ferlay J**, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, Gavin A, Visser O, Bray F. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer* 2018; **103**: 356-387 [PMID: 30100160 DOI: 10.1016/j.ejca.2018.07.005]
- 2 **Shi T**, Gao G, Cao Y. Long Noncoding RNAs as Novel Biomarkers Have a Promising Future in Cancer Diagnostics. *Dis Markers* 2016; **2016**: 9085195 [PMID: 27143813 DOI: 10.1155/2016/9085195]
- 3 **Gutschner T**, Diederichs S. The hallmarks of cancer: a long non-coding RNA point of view. *RNA Biol* 2012; **9**: 703-719 [PMID: 22664915 DOI: 10.4161/rna.20481]
- 4 **Ma Y**, Yang Y, Wang F, Moyer MP, Wei Q, Zhang P, Yang Z, Liu W, Zhang H, Chen N, Wang H, Wang H, Qin H. Long non-coding RNA CCAL regulates colorectal cancer progression by activating Wnt/ β -catenin signalling pathway via suppression of activator protein 2 α . *Gut* 2016; **65**: 1494-1504 [PMID: 25994219 DOI: 10.1136/gutjnl-2014-308392]
- 5 **Zhang H**, Chen Z, Wang X, Huang Z, He Z, Chen Y. Long non-coding RNA: a new player in cancer. *J Hematol Oncol* 2013; **6**: 37 [PMID: 23725405 DOI: 10.1186/1756-8722-6-37]
- 6 **Qiu MT**, Hu JW, Yin R, Xu L. Long noncoding RNA: an emerging paradigm of cancer research. *Tumour Biol* 2013; **34**: 613-620 [PMID: 23359273 DOI: 10.1007/s13277-013-0658-6]
- 7 **Ji Q**, Liu X, Fu X, Zhang L, Sui H, Zhou L, Sun J, Cai J, Qin J, Ren J, Li Q. Resveratrol inhibits invasion and metastasis of colorectal cancer cells via MALAT1 mediated Wnt/ β -catenin signal pathway. *PLoS One* 2013; **8**: e78700 [PMID: 24244343 DOI: 10.1371/journal.pone.0078700]
- 8 **Yue B**, Liu C, Sun H, Liu M, Song C, Cui R, Qiu S, Zhong M. A Positive Feed-Forward Loop between LncRNA-CYTOR and Wnt/ β -Catenin Signaling Promotes Metastasis of Colon Cancer. *Mol Ther* 2018; **26**: 1287-1298 [PMID: 29606502 DOI: 10.1016/j.ymthe.2018.02.024]
- 9 **Xu S**, Sui S, Zhang J, Bai N, Shi Q, Zhang G, Gao S, You Z, Zhan C, Liu F, Pang D. Downregulation of long noncoding RNA MALAT1 induces epithelial-to-mesenchymal transition via the PI3K-AKT pathway in breast cancer. *Int J Clin Exp Pathol* 2015; **8**: 4881-4891 [PMID: 26191181]
- 10 **Zhou J**, Zhi X, Wang L, Wang W, Li Z, Tang J, Wang J, Zhang Q, Xu Z. Linc00152 promotes proliferation in gastric cancer through the EGFR-dependent pathway. *J Exp Clin Cancer Res* 2015; **34**: 135 [PMID: 26538117 DOI: 10.1186/s13046-015-0250-6]
- 11 **Yue B**, Cai D, Liu C, Fang C, Yan D. Linc00152 Functions as a Competing Endogenous RNA to Confer Oxaliplatin Resistance and Holds Prognostic Values in Colon Cancer. *Mol Ther* 2016; **24**: 2064-2077 [PMID: 27633443 DOI: 10.1038/mt.2016.180]
- 12 **Cai Q**, Wang ZQ, Wang SH, Li C, Zhu ZG, Quan ZW, Zhang WJ. Upregulation of long non-coding RNA LINC00152 by SP1 contributes to gallbladder cancer cell growth and tumor metastasis via PI3K/AKT pathway. *Am J Transl Res* 2016; **8**: 4068-4081 [PMID: 27829993]
- 13 **Bian Z**, Zhang J, Li M, Feng Y, Yao S, Song M, Qi X, Fei B, Yin Y, Hua D, Huang Z. Correction: Long non-coding RNA LINC00152 promotes cell proliferation, metastasis, and confers 5-FU resistance in colorectal cancer by inhibiting miR-139-5p. *Oncogenesis* 2018; **7**: 63 [PMID: 30115914 DOI: 10.1038/s41389-018-0067-1]
- 14 **Yang X**, Duan B, Zhou X. Long non-coding RNA FOXD2-AS1 functions as a tumor promoter in colorectal cancer by regulating EMT and Notch signaling pathway. *Eur Rev Med Pharmacol Sci* 2017; **21**: 3586-3591 [PMID: 28925486]
- 15 **Lu S**, Dong W, Zhao P, Liu Z. lncRNA FAM83H-AS1 is associated with the prognosis of colorectal carcinoma and promotes cell proliferation by targeting the Notch signaling pathway. *Oncol Lett* 2018; **15**: 1861-1868 [PMID: 29434883 DOI: 10.3892/ol.2017.7520]
- 16 **Ji J**, Tang J, Deng L, Xie Y, Jiang R, Li G, Sun B. LINC00152 promotes proliferation in hepatocellular carcinoma by targeting EpCAM via the mTOR signaling pathway. *Oncotarget* 2015; **6**: 42813-42824 [PMID: 26540343 DOI: 10.18632/oncotarget.5970]
- 17 **Jahangiri B**, Khalaj-Kondori M, Asadollahi E, Sadeghizadeh M. Cancer-associated fibroblasts enhance cell proliferation and metastasis of colorectal cancer SW480 cells by provoking long noncoding RNA UCA1. *J Cell Commun Signal* 2019; **13**: 53-64 [PMID: 29948578 DOI: 10.1007/s12079-018-0471-5]
- 18 **Sun L**, Jiang C, Xu C, Xue H, Zhou H, Gu L, Liu Y, Xu Q. Down-regulation of long non-coding RNA RP11-708H21.4 is associated with poor prognosis for colorectal cancer and promotes tumorigenesis through regulating AKT/mTOR pathway. *Oncotarget* 2017; **8**: 27929-27942 [PMID: 28427191 DOI: 10.18632/oncotarget.15846]
- 19 **Thorenoor N**, Faltejkskova-Vychytilova P, Hombach S, Mlcochova J, Kretz M, Svoboda M, Slaby O. Long non-coding RNA ZFAS1 interacts with CDK1 and is involved in p53-dependent cell cycle control and apoptosis in colorectal cancer. *Oncotarget* 2016; **7**: 622-637 [PMID: 26506418 DOI: 10.18632/oncotarget.5807]
- 20 **Yang P**, Yang Y, An W, Xu J, Zhang G, Jie J, Zhang Q. The long noncoding RNA-ROR promotes the resistance of radiotherapy for human colorectal cancer cells by targeting the p53/miR-145 pathway. *J Gastroenterol Hepatol* 2017; **32**: 837-845 [PMID: 27696511 DOI: 10.1111/jgh.13606]
- 21 **Qi P**, Zhou XY, Du X. Circulating long non-coding RNAs in cancer: current status and future perspectives. *Mol Cancer* 2016; **15**: 39 [PMID: 27189224 DOI: 10.1186/s12943-016-0524-4]
- 22 **Yang Y**, Junjie P, Sanjun C, Ma Y. Long non-coding RNAs in Colorectal Cancer: Progression and Future Directions. *J Cancer* 2017; **8**: 3212-3225 [PMID: 29158793 DOI: 10.7150/jca.19794]
- 23 **Alaiyan B**, Ilyayev N, Stojadinovic A, Izadjoo M, Roistacher M, Pavlov V, Tzivin V, Halle D, Pan H, Trink B, Gure AO, Nissan A. Differential expression of colon cancer associated transcript1 (CCAT1) along the colonic adenoma-carcinoma sequence. *BMC Cancer* 2013; **13**: 196 [PMID: 23594791 DOI: 10.1186/1471-2407-13-196]
- 24 **Graham LD**, Pedersen SK, Brown GS, Ho T, Kassir Z, Moynihan AT, Vizgoft EK, Dunne R, Pimlott L, Young GP, Lapointe LC, Molloy PL. Colorectal Neoplasia Differentially Expressed (CRNDE), a Novel Gene with Elevated Expression in Colorectal Adenomas and Adenocarcinomas. *Genes Cancer* 2011; **2**: 829-840 [PMID: 22393467 DOI: 10.1177/1947601911431081]
- 25 **Pachnis V**, Belayew A, Tilghman SM. Locus unlinked to alpha-fetoprotein under the control of the murine raf and Rif genes. *Proc Natl Acad Sci USA* 1984; **81**: 5523-5527 [PMID: 6206499 DOI: 10.1073/pnas.81.17.5523]
- 26 **Borsani G**, Tonlorenzi R, Simmler MC, Dandolo L, Arnaud D, Capra V, Grompe M, Pizzuti A, Muzny D, Lawrence C, Willard HF, Avner P, Ballabio A. Characterization of a murine gene expressed from the inactive X chromosome. *Nature* 1991; **351**: 325-329 [PMID: 2034278 DOI: 10.1038/351325a0]
- 27 **Jarroux J**, Morillon A, Pinskaya M. History, Discovery, and Classification of lncRNAs. *Adv Exp Med Biol* 2017; **1008**: 1-46 [PMID: 28815535 DOI: 10.1007/978-981-10-5203-3_1]
- 28 **Kung JT**, Colognori D, Lee JT. Long noncoding RNAs: past, present, and future. *Genetics* 2013; **193**:

- 651-669 [PMID: [23463798](#) DOI: [10.1534/genetics.112.146704](#)]
- 29 **Gloss BS**, Dinger ME. Realizing the significance of noncoding functionality in clinical genomics. *Exp Mol Med* 2018; **50**: 97 [PMID: [30089779](#) DOI: [10.1038/s12276-018-0087-0](#)]
 - 30 **Cheng L**, Wang P, Tian R, Wang S, Guo Q, Luo M, Zhou W, Liu G, Jiang H, Jiang Q. LncRNA2Target v2.0: a comprehensive database for target genes of lncRNAs in human and mouse. *Nucleic Acids Res* 2019; **47**: D140-D144 [PMID: [30380072](#) DOI: [10.1093/nar/gky1051](#)]
 - 31 **Lee RC**, Feinbaum RL, Ambros V. The *C. elegans* heterochronic gene *lin-4* encodes small RNAs with antisense complementarity to *lin-14*. *Cell* 1993; **75**: 843-854 [PMID: [8252621](#)]
 - 32 **Mercer TR**, Dinger ME, Mattick JS. Long non-coding RNAs: insights into functions. *Nat Rev Genet* 2009; **10**: 155-159 [PMID: [19188922](#) DOI: [10.1038/nrg2521](#)]
 - 33 **Ulitsky I**, Bartel DP. lincRNAs: genomics, evolution, and mechanisms. *Cell* 2013; **154**: 26-46 [PMID: [23827673](#) DOI: [10.1016/j.cell.2013.06.020](#)]
 - 34 **Pelechano V**, Steinmetz LM. Gene regulation by antisense transcription. *Nat Rev Genet* 2013; **14**: 880-893 [PMID: [24217315](#) DOI: [10.1038/nrg3594](#)]
 - 35 **Ma L**, Bajic VB, Zhang Z. On the classification of long non-coding RNAs. *RNA Biol* 2013; **10**: 925-933 [PMID: [23696037](#) DOI: [10.4161/rna.24604](#)]
 - 36 **Katayama S**, Tomaru Y, Kasukawa T, Waki K, Nakanishi M, Nakamura M, Nishida H, Yap CC, Suzuki M, Kawai J, Suzuki H, Carninci P, Hayashizaki Y, Wells C, Frith M, Ravasi T, Pang KC, Hallinan J, Mattick J, Hume DA, Lipovich L, Batalov S, Engström PG, Mizuno Y, Faghihi MA, Sandelin A, Chalk AM, Mottagui-Tabar S, Liang Z, Lenhard B, Wahlestedt C, RIKEN Genome Exploration Research Group; Genome Science Group (Genome Network Project Core Group); FANTOM Consortium. Antisense transcription in the mammalian transcriptome. *Science* 2005; **309**: 1564-1566 [PMID: [16141073](#) DOI: [10.1126/science.1112009](#)]
 - 37 **He Y**, Vogelstein B, Velculescu VE, Papadopoulos N, Kinzler KW. The antisense transcriptomes of human cells. *Science* 2008; **322**: 1855-1857 [PMID: [19056939](#) DOI: [10.1126/science.1163853](#)]
 - 38 **Lee JT**, Davidow LS, Warshawsky D. Tsix, a gene antisense to Xist at the X-inactivation centre. *Nat Genet* 1999; **21**: 400-404 [PMID: [10192391](#) DOI: [10.1038/7734](#)]
 - 39 **Balakirev ES**, Ayala FJ. Pseudogenes: are they "junk" or functional DNA? *Annu Rev Genet* 2003; **37**: 123-151 [PMID: [14616058](#) DOI: [10.1146/annurev.genet.37.040103.103949](#)]
 - 40 **St Laurent G**, Wahlestedt C, Kapranov P. The Landscape of long noncoding RNA classification. *Trends Genet* 2015; **31**: 239-251 [PMID: [25869999](#) DOI: [10.1016/j.tig.2015.03.007](#)]
 - 41 **Geisler S**, Collier J. RNA in unexpected places: long non-coding RNA functions in diverse cellular contexts. *Nat Rev Mol Cell Biol* 2013; **14**: 699-712 [PMID: [24105322](#) DOI: [10.1038/nrm3679](#)]
 - 42 **Gudenas BL**, Wang L. Prediction of lncRNA Subcellular Localization with Deep Learning from Sequence Features. *Sci Rep* 2018; **8**: 16385 [PMID: [30401954](#) DOI: [10.1038/s41598-018-34708-w](#)]
 - 43 **Cech TR**, Steitz JA. The noncoding RNA revolution-trashing old rules to forge new ones. *Cell* 2014; **157**: 77-94 [PMID: [24679528](#) DOI: [10.1016/j.cell.2014.03.008](#)]
 - 44 **Long Y**, Wang X, Youmans DT, Cech TR. How do lncRNAs regulate transcription? *Sci Adv* 2017; **3**: eaao2110 [PMID: [28959731](#) DOI: [10.1126/sciadv.aao2110](#)]
 - 45 **Kornienko AE**, Guenzl PM, Barlow DP, Pauler FM. Gene regulation by the act of long non-coding RNA transcription. *BMC Biol* 2013; **11**: 59 [PMID: [23721193](#) DOI: [10.1186/1741-7007-11-59](#)]
 - 46 **Yao RW**, Wang Y, Chen LL. Cellular functions of long noncoding RNAs. *Nat Cell Biol* 2019; **21**: 542-551 [PMID: [31048766](#) DOI: [10.1038/s41556-019-0311-8](#)]
 - 47 **Yang S**, Sun Z, Zhou Q, Wang W, Wang G, Song J, Li Z, Zhang Z, Chang Y, Xia K, Liu J, Yuan W. MicroRNAs, long noncoding RNAs, and circular RNAs: potential tumor biomarkers and targets for colorectal cancer. *Cancer Manag Res* 2018; **10**: 2249-2257 [PMID: [30100756](#) DOI: [10.2147/CMAR.S166308](#)]
 - 48 **Romero-Barrios N**, Legascue MF, Benhamed M, Ariel F, Crespi M. Splicing regulation by long noncoding RNAs. *Nucleic Acids Res* 2018; **46**: 2169-2184 [PMID: [29425321](#) DOI: [10.1093/nar/gky095](#)]
 - 49 **Willingham AT**, Orth AP, Batalov S, Peters EC, Wen BG, Aza-Blanc P, Hogenesch JB, Schultz PG. A strategy for probing the function of noncoding RNAs finds a repressor of NFAT. *Science* 2005; **309**: 1570-1573 [PMID: [16141075](#) DOI: [10.1126/science.1115901](#)]
 - 50 **Staněk D**, Fox AH. Nuclear bodies: new insights into structure and function. *Curr Opin Cell Biol* 2017; **46**: 94-101 [PMID: [28577509](#) DOI: [10.1016/j.ceb.2017.05.001](#)]
 - 51 **Chujo T**, Yamazaki T, Hirose T. Architectural RNAs (arcRNAs): A class of long noncoding RNAs that function as the scaffold of nuclear bodies. *Biochim Biophys Acta* 2016; **1859**: 139-146 [PMID: [26021608](#) DOI: [10.1016/j.bbagr.2015.05.007](#)]
 - 52 **Clemson CM**, Hutchinson JN, Sara SA, Ensminger AW, Fox AH, Chess A, Lawrence JB. An architectural role for a nuclear noncoding RNA: NEAT1 RNA is essential for the structure of paraspeckles. *Mol Cell* 2009; **33**: 717-726 [PMID: [19217333](#) DOI: [10.1016/j.molcel.2009.01.026](#)]
 - 53 **Tsai MC**, Manor O, Wan Y, Mosammamaparast N, Wang JK, Lan F, Shi Y, Segal E, Chang HY. Long noncoding RNA as modular scaffold of histone modification complexes. *Science* 2010; **329**: 689-693 [PMID: [20616235](#) DOI: [10.1126/science.1192002](#)]
 - 54 **Merry CR**, Forrest ME, Sabers JN, Beard L, Gao XH, Hatzoglou M, Jackson MW, Wang Z, Markowitz SD, Khalil AM. DNMT1-associated long non-coding RNAs regulate global gene expression and DNA methylation in colon cancer. *Hum Mol Genet* 2015; **24**: 6240-6253 [PMID: [26307088](#) DOI: [10.1093/hmg/ddv343](#)]
 - 55 **Zhao Y**, Sun H, Wang H. Long noncoding RNAs in DNA methylation: new players stepping into the old game. *Cell Biosci* 2016; **6**: 45 [PMID: [27408682](#) DOI: [10.1186/s13578-016-0109-3](#)]
 - 56 **Clark MB**, Johnston RL, Inostroza-Ponta M, Fox AH, Fortini E, Moscatto P, Dinger ME, Mattick JS. Genome-wide analysis of long noncoding RNA stability. *Genome Res* 2012; **22**: 885-898 [PMID: [22406755](#) DOI: [10.1101/gr.131037.111](#)]
 - 57 **Sharova LV**, Sharov AA, Nedorezov T, Piao Y, Shaik N, Ko MS. Database for mRNA half-life of 19 977 genes obtained by DNA microarray analysis of pluripotent and differentiating mouse embryonic stem cells. *DNA Res* 2009; **16**: 45-58 [PMID: [19001483](#) DOI: [10.1093/dnares/dsn030](#)]
 - 58 **Tani H**, Mizutani R, Salam KA, Tano K, Ijiri K, Wakamatsu A, Isogai T, Suzuki Y, Akimitsu N. Genome-wide determination of RNA stability reveals hundreds of short-lived noncoding transcripts in mammals. *Genome Res* 2012; **22**: 947-956 [PMID: [22369889](#) DOI: [10.1101/gr.130559.111](#)]
 - 59 **Zampetaki A**, Albrecht A, Steinhofel K. Long Non-coding RNA Structure and Function: Is There a Link? *Front Physiol* 2018; **9**: 1201 [PMID: [30197605](#) DOI: [10.3389/fphys.2018.01201](#)]
 - 60 **Dinger ME**, Amaral PP, Mercer TR, Mattick JS. Pervasive transcription of the eukaryotic genome:

- functional indices and conceptual implications. *Brief Funct Genomic Proteomic* 2009; **8**: 407-423 [PMID: 19770204 DOI: 10.1093/bfpg/elp038]
- 61 **Mao YS**, Sunwoo H, Zhang B, Spector DL. Direct visualization of the co-transcriptional assembly of a nuclear body by noncoding RNAs. *Nat Cell Biol* 2011; **13**: 95-101 [PMID: 21170033 DOI: 10.1038/ncb2140]
- 62 **Charles Richard JL**, Eichhorn PJA. Platforms for Investigating lncRNA Functions. *SLAS Technol* 2018; **23**: 493-506 [PMID: 29945466 DOI: 10.1177/2472630318780639]
- 63 **Velculescu VE**, Zhang L, Vogelstein B, Kinzler KW. Serial analysis of gene expression. *Science* 1995; **270**: 484-487 [PMID: 7570003]
- 64 **Kashi K**, Henderson L, Bonetti A, Carninci P. Discovery and functional analysis of lncRNAs: Methodologies to investigate an uncharacterized transcriptome. *Biochim Biophys Acta* 2016; **1859**: 3-15 [PMID: 26477492 DOI: 10.1016/j.bbagr.2015.10.010]
- 65 **Wang Z**, Gerstein M, Snyder M. RNA-Seq: a revolutionary tool for transcriptomics. *Nat Rev Genet* 2009; **10**: 57-63 [PMID: 19015660 DOI: 10.1038/nrg2484]
- 66 **Shiraki T**, Kondo S, Katayama S, Waki K, Kasukawa T, Kawaji H, Kodzius R, Watahiki A, Nakamura M, Arakawa T, Fukuda S, Sasaki D, Podhajski A, Harbers M, Kawai J, Carninci P, Hayashizaki Y. Cap analysis gene expression for high-throughput analysis of transcriptional starting point and identification of promoter usage. *Proc Natl Acad Sci USA* 2003; **100**: 15776-15781 [PMID: 14663149 DOI: 10.1073/pnas.2136655100]
- 67 **Ma J**, Chen Q, Ma D. Biological Functions and Research Methods of Long Noncoding RNAs. *Shengzhi Yu Biyun* 2017; **1**: 23-29
- 68 **Ferrè F**, Colantoni A, Helmer-Citterich M. Revealing protein-lncRNA interaction. *Brief Bioinform* 2016; **17**: 106-116 [PMID: 26041786 DOI: 10.1093/bib/bbv031]
- 69 **Uren PJ**, Bahrami-Samani E, Burns SC, Qiao M, Karginov FV, Hodges E, Hannon GJ, Sanford JR, Penalva LO, Smith AD. Site identification in high-throughput RNA-protein interaction data. *Bioinformatics* 2012; **28**: 3013-3020 [PMID: 23024010 DOI: 10.1093/bioinformatics/bts569]
- 70 **König J**, Zarnack K, Rot G, Curk T, Kayikci M, Zupan B, Turner DJ, Luscombe NM, Ule J. iCLIP--transcriptome-wide mapping of protein-RNA interactions with individual nucleotide resolution. *J Vis Exp* 2011 [PMID: 21559008 DOI: 10.3791/2638]
- 71 **Chu C**, Quinn J, Chang HY. Chromatin isolation by RNA purification (ChIRP). *J Vis Exp* 2012; pii: 3912 [PMID: 22472705 DOI: 10.3791/3912]
- 72 **Simon MD**, Wang CI, Kharchenko PV, West JA, Chapman BA, Alekseyenko AA, Borowsky ML, Kuroda MI, Kingston RE. The genomic binding sites of a noncoding RNA. *Proc Natl Acad Sci USA* 2011; **108**: 20497-20502 [PMID: 22143764 DOI: 10.1073/pnas.1113536108]
- 73 **Engreitz J**, Lander ES, Guttman M. RNA antisense purification (RAP) for mapping RNA interactions with chromatin. *Methods Mol Biol* 2015; **1262**: 183-197 [PMID: 25555582 DOI: 10.1007/978-1-4939-2253-6_11]
- 74 **Engreitz JM**, Sirokman K, McDonel P, Shishkin AA, Surka C, Russell P, Grossman SR, Chow AY, Guttman M, Lander ES. RNA-RNA interactions enable specific targeting of noncoding RNAs to nascent Pre-mRNAs and chromatin sites. *Cell* 2014; **159**: 188-199 [PMID: 25259926 DOI: 10.1016/j.cell.2014.08.018]
- 75 **Kudla G**, Granneman S, Hahn D, Beggs JD, Tollervey D. Cross-linking, ligation, and sequencing of hybrids reveals RNA-RNA interactions in yeast. *Proc Natl Acad Sci USA* 2011; **108**: 10010-10015 [PMID: 21610164 DOI: 10.1073/pnas.1017386108]
- 76 **Wan Y**, Kertesz M, Spitale RC, Segal E, Chang HY. Understanding the transcriptome through RNA structure. *Nat Rev Genet* 2011; **12**: 641-655 [PMID: 21850044 DOI: 10.1038/nrg3049]
- 77 **Shah S**, Takei Y, Zhou W, Lubeck E, Yun J, Eng CL, Koulina N, Cronin C, Karp C, Liaw EJ, Amin M, Cai L. Dynamics and Spatial Genomics of the Nascent Transcriptome by Intron seqFISH. *Cell* 2018; **174**: 363-376.e16 [PMID: 29887381 DOI: 10.1016/j.cell.2018.05.035]
- 78 **Chen KH**, Boettiger AN, Moffitt JR, Wang S, Zhuang X. RNA imaging. Spatially resolved, highly multiplexed RNA profiling in single cells. *Science* 2015; **348**: aaa6090 [PMID: 25858977 DOI: 10.1126/science.aaa6090]
- 79 **Cabili MN**, Dunagin MC, McClanahan PD, Biaisch A, Padovan-Merhar O, Regev A, Rinn JL, Raj A. Localization and abundance analysis of human lncRNAs at single-cell and single-molecule resolution. *Genome Biol* 2015; **16**: 20 [PMID: 25630241 DOI: 10.1186/s13059-015-0586-4]
- 80 **Gustafsson MG**. Nonlinear structured-illumination microscopy: wide-field fluorescence imaging with theoretically unlimited resolution. *Proc Natl Acad Sci U S A* 2005; **102**: 13081-13086 [PMID: 16141335 DOI: 10.1073/pnas.0406877102]
- 81 **Rust MJ**, Bates M, Zhuang X. Sub-diffraction-limit imaging by stochastic optical reconstruction microscopy (STORM). *Nat Methods* 2006; **3**: 793-795 [PMID: 16896339 DOI: 10.1038/nmeth929]
- 82 **Dias N**, Stein CA. Potential roles of antisense oligonucleotides in cancer therapy. The example of Bcl-2 antisense oligonucleotides. *Eur J Pharm Biopharm* 2002; **54**: 263-269 [PMID: 12445555]
- 83 **Jinek M**, Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentier E. A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. *Science* 2012; **337**: 816-821 [PMID: 22745249 DOI: 10.1126/science.1225829]
- 84 **Liu SJ**, Horlbeck MA, Cho SW, Birk HS, Malatesta M, He D, Attenello FJ, Villalta JE, Cho MY, Chen Y, Mandegar MA, Olvera MP, Gilbert LA, Conklin BR, Chang HY, Weissman JS, Lim DA. CRISPRi-based genome-scale identification of functional long noncoding RNA loci in human cells. *Science* 2017; **355** [PMID: 27980086 DOI: 10.1126/science.aah7111]
- 85 **Bester AC**, Lee JD, Chavez A, Lee YR, Nachmani D, Vora S, Victor J, Sauvageau M, Monteleone E, Rinn JL, Provero P, Church GM, Clohessy JG, Pandolfi PP. An Integrated Genome-wide CRISPRa Approach to Functionalize lncRNAs in Drug Resistance. *Cell* 2018; **173**: 649-664.e20 [PMID: 29677511 DOI: 10.1016/j.cell.2018.03.052]
- 86 **Gilbert LA**, Horlbeck MA, Adamson B, Villalta JE, Chen Y, Whitehead EH, Guimaraes C, Panning B, Ploegh HL, Bassik MC, Qi LS, Kampmann M, Weissman JS. Genome-Scale CRISPR-Mediated Control of Gene Repression and Activation. *Cell* 2014; **159**: 647-661 [PMID: 25307932 DOI: 10.1016/j.cell.2014.09.029]
- 87 **Gupta RA**, Shah N, Wang KC, Kim J, Horlings HM, Wong DJ, Tsai MC, Hung T, Argani P, Rinn JL, Wang Y, Brzoska P, Kong B, Li R, West RB, van de Vijver MJ, Sukumar S, Chang HY. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. *Nature* 2010; **464**: 1071-1076 [PMID: 20393566 DOI: 10.1038/nature08975]

- 88 **Wu ZH**, Wang XL, Tang HM, Jiang T, Chen J, Lu S, Qiu GQ, Peng ZH, Yan DW. Long non-coding RNA HOTAIR is a powerful predictor of metastasis and poor prognosis and is associated with epithelial-mesenchymal transition in colon cancer. *Oncol Rep* 2014; **32**: 395-402 [PMID: [24840737](#) DOI: [10.3892/or.2014.3186](#)]
- 89 **Kogo R**, Shimamura T, Mimori K, Kawahara K, Imoto S, Sudo T, Tanaka F, Shibata K, Suzuki A, Komune S, Miyano S, Mori M. Long noncoding RNA HOTAIR regulates polycomb-dependent chromatin modification and is associated with poor prognosis in colorectal cancers. *Cancer Res* 2011; **71**: 6320-6326 [PMID: [21862635](#) DOI: [10.1158/0008-5472.CAN-11-1021](#)]
- 90 **Svoboda M**, Slysokova J, Schneiderova M, Makovicky P, Bielik L, Levy M, Lipska L, Hemmelova B, Kala Z, Protivankova M, Vycital O, Liska V, Schwarzova L, Vodickova L, Vodicka P. HOTAIR long non-coding RNA is a negative prognostic factor not only in primary tumors, but also in the blood of colorectal cancer patients. *Carcinogenesis* 2014; **35**: 1510-1515 [PMID: [24583926](#) DOI: [10.1093/carcin/bgu055](#)]
- 91 **Xu C**, Yang M, Tian J, Wang X, Li Z. MALAT-1: a long non-coding RNA and its important 3' end functional motif in colorectal cancer metastasis. *Int J Oncol* 2011; **39**: 169-175 [PMID: [21503572](#) DOI: [10.3892/ijo.2011.1007](#)]
- 92 **Zheng HT**, Shi DB, Wang YW, Li XX, Xu Y, Tripathi P, Gu WL, Cai GX, Cai SJ. High expression of lncRNA MALAT1 suggests a biomarker of poor prognosis in colorectal cancer. *Int J Clin Exp Pathol* 2014; **7**: 3174-3181 [PMID: [25031737](#)]
- 93 **Ji Q**, Zhang L, Liu X, Zhou L, Wang W, Han Z, Sui H, Tang Y, Wang Y, Liu N, Ren J, Hou F, Li Q. Long non-coding RNA MALAT1 promotes tumour growth and metastasis in colorectal cancer through binding to SFPQ and releasing oncogene PTBP2 from SFPQ/PTBP2 complex. *Br J Cancer* 2014; **111**: 736-748 [PMID: [25025966](#) DOI: [10.1038/bjc.2014.383](#)]
- 94 **Tsang WP**, Ng EK, Ng SS, Jin H, Yu J, Sung JJ, Kwok TT. Oncofetal H19-derived miR-675 regulates tumor suppressor RB in human colorectal cancer. *Carcinogenesis* 2010; **31**: 350-358 [PMID: [19926638](#) DOI: [10.1093/carcin/bgp181](#)]
- 95 **Yang W**, Ning N, Jin X. The lncRNA H19 Promotes Cell Proliferation by Competitively Binding to miR-200a and Derepressing β -Catenin Expression in Colorectal Cancer. *Biomed Res Int* 2017; **2017**: 2767484 [PMID: [28164117](#) DOI: [10.1155/2017/2767484](#)]
- 96 **Nissan A**, Stojadinovic A, Mitrani-Rosenbaum S, Halle D, Grinbaum R, Roistacher M, Bochem A, Dayanc BE, Ritter G, Gomceli I, Bostanci EB, Akoglu M, Chen YT, Old LJ, Gure AO. Colon cancer associated transcript-1: a novel RNA expressed in malignant and pre-malignant human tissues. *Int J Cancer* 2012; **130**: 1598-1606 [PMID: [21547902](#) DOI: [10.1002/ijc.26170](#)]
- 97 **He X**, Tan X, Wang X, Jin H, Liu L, Ma L, Yu H, Fan Z. C-Myc-activated long noncoding RNA CCAT1 promotes colon cancer cell proliferation and invasion. *Tumour Biol* 2014; **35**: 12181-12188 [PMID: [25185650](#) DOI: [10.1007/s13277-014-2526-4](#)]
- 98 **Xie X**, Tang B, Xiao YF, Xie R, Li BS, Dong H, Zhou JY, Yang SM. Long non-coding RNAs in colorectal cancer. *Oncotarget* 2016; **7**: 5226-5239 [PMID: [26637808](#) DOI: [10.18632/oncotarget.6446](#)]
- 99 **Liu T**, Zhang X, Yang YM, Du LT, Wang CX. Increased expression of the long noncoding RNA CRNDE-h indicates a poor prognosis in colorectal cancer, and is positively correlated with IRX5 mRNA expression. *Onco Targets Ther* 2016; **9**: 1437-1448 [PMID: [27042112](#) DOI: [10.2147/ott.s98268](#)]
- 100 **Yamada A**, Yu P, Lin W, Okugawa Y, Boland CR, Goel A. A RNA-Sequencing approach for the identification of novel long non-coding RNA biomarkers in colorectal cancer. *Sci Rep* 2018; **8**: 575 [PMID: [29330370](#) DOI: [10.1038/s41598-017-18407-6](#)]
- 101 **Barbagallo C**, Brex D, Caponnetto A, Cirmigliaro M, Scalia M, Magnano A, Caltabiano R, Barbagallo D, Biondi A, Cappellani A, Basile F, Di Pietro C, Purrello M, Ragusa M. LncRNA UCA1, Upregulated in CRC Biopsies and Downregulated in Serum Exosomes, Controls mRNA Expression by RNA-RNA Interactions. *Mol Ther Nucleic Acids* 2018; **12**: 229-241 [PMID: [30195762](#) DOI: [10.1016/j.omtn.2018.05.009](#)]
- 102 **Kalmar A**, Nagy ZB, Galamb O, Csabai I, Bodor A, Wichmann B, Valez G, Bartak BK, Tulassay Z, Igaz P, Molnar B. Genome-wide expression profiling in colorectal cancer focusing on lncRNAs in the adenoma-carcinoma transition. *BMC Cancer* 2019; In press
- 103 **Liu T**, Zhang X, Gao S, Jing F, Yang Y, Du L, Zheng G, Li P, Li C, Wang C. Exosomal long noncoding RNA CRNDE-h as a novel serum-based biomarker for diagnosis and prognosis of colorectal cancer. *Oncotarget* 2016; **7**: 85551-85563 [PMID: [27888803](#) DOI: [10.18632/oncotarget.13465](#)]
- 104 **Ding J**, Li J, Wang H, Tian Y, Xie M, He X, Ji H, Ma Z, Hui B, Wang K, Ji G. Long noncoding RNA CRNDE promotes colorectal cancer cell proliferation via epigenetically silencing DUSP5/CDKN1A expression. *Cell Death Dis* 2017; **8**: e2997 [PMID: [28796262](#) DOI: [10.1038/cddis.2017.328](#)]
- 105 **Jiang H**, Wang Y, Ai M, Wang H, Duan Z, Wang H, Zhao L, Yu J, Ding Y, Wang S. Long noncoding RNA CRNDE stabilized by hnRNPUL2 accelerates cell proliferation and migration in colorectal carcinoma via activating Ras/MAPK signaling pathways. *Cell Death Dis* 2017; **8**: e2862 [PMID: [28594403](#) DOI: [10.1038/cddis.2017.258](#)]
- 106 **Yu B**, Ye X, Du Q, Zhu B, Zhai Q, Li XX. The Long Non-Coding RNA CRNDE Promotes Colorectal Carcinoma Progression by Competitively Binding miR-217 with TCF7L2 and Enhancing the Wnt/ β -Catenin Signaling Pathway. *Cell Physiol Biochem* 2017; **41**: 2489-2502 [PMID: [28472810](#) DOI: [10.1159/000475941](#)]
- 107 **Han P**, Li JW, Zhang BM, Lv JC, Li YM, Gu XY, Yu ZW, Jia YH, Bai XF, Li L, Liu YL, Cui BB. The lncRNA CRNDE promotes colorectal cancer cell proliferation and chemoresistance via miR-181a-5p-mediated regulation of Wnt/ β -catenin signaling. *Mol Cancer* 2017; **16**: 9 [PMID: [28086904](#) DOI: [10.1186/s12943-017-0583-1](#)]
- 108 **Gao H**, Song X, Kang T, Yan B, Feng L, Gao L, Ai L, Liu X, Yu J, Li H. Long noncoding RNA CRNDE functions as a competing endogenous RNA to promote metastasis and oxaliplatin resistance by sponging miR-136 in colorectal cancer. *Onco Targets Ther* 2017; **10**: 205-216 [PMID: [28115855](#) DOI: [10.2147/OTT.S116178](#)]
- 109 **Tao K**, Yang J, Hu Y, Sun Y, Tan Z, Duan J, Zhang F, Yan H, Deng A. Clinical significance of urothelial carcinoma associated 1 in colon cancer. *Int J Clin Exp Med* 2015; **8**: 21854-21860 [PMID: [26885155](#)]
- 110 **Han Y**, Yang YN, Yuan HH, Zhang TT, Sui H, Wei XL, Liu L, Huang P, Zhang WJ, Bai YX. UCA1, a long non-coding RNA up-regulated in colorectal cancer influences cell proliferation, apoptosis and cell cycle distribution. *Pathology* 2014; **46**: 396-401 [PMID: [24977734](#) DOI: [10.1097/PAT.0000000000000125](#)]
- 111 **Lao Y**, Li Q, Li N, Liu H, Liu K, Jiang G, Wei N, Wang C, Wang Y, Wu J. Long noncoding RNA ENST00000455974 plays an oncogenic role through up-regulating JAG2 in human DNA mismatch repair-

- proficient colon cancer. *Biochem Biophys Res Commun* 2019; **508**: 339-347 [PMID: [30473216](#) DOI: [10.1016/j.bbrc.2018.11.088](#)]
- 112 **Sole C**, Arnaiz E, Manterola L, Otaegui D, Lawrie CH. The circulating transcriptome as a source of cancer liquid biopsy biomarkers. *Semin Cancer Biol* 2019 [PMID: [30684535](#) DOI: [10.1016/j.semcancer.2019.01.003](#)]
 - 113 **Li Q**, Shao Y, Zhang X, Zheng T, Miao M, Qin L, Wang B, Ye G, Xiao B, Guo J. Plasma long noncoding RNA protected by exosomes as a potential stable biomarker for gastric cancer. *Tumour Biol* 2015; **36**: 2007-2012 [PMID: [25391424](#) DOI: [10.1007/s13277-014-2807-y](#)]
 - 114 **Viereck J**, Thum T. Circulating Noncoding RNAs as Biomarkers of Cardiovascular Disease and Injury. *Circ Res* 2017; **120**: 381-399 [PMID: [28104771](#) DOI: [10.1161/CIRCRESAHA.116.308434](#)]
 - 115 **Chen D**, Sun Q, Cheng X, Zhang L, Song W, Zhou D, Lin J, Wang W. Genome-wide analysis of long noncoding RNA (lncRNA) expression in colorectal cancer tissues from patients with liver metastasis. *Cancer Med* 2016; **5**: 1629-1639 [PMID: [27165481](#) DOI: [10.1002/cam4.738](#)]
 - 116 **Zhao W**, Song M, Zhang J, Kuerban M, Wang H. Combined identification of long non-coding RNA CCAT1 and HOTAIR in serum as an effective screening for colorectal carcinoma. *Int J Clin Exp Pathol* 2015; **8**: 14131-14140 [PMID: [26823726](#)]
 - 117 **Wan L**, Kong J, Tang J, Wu Y, Xu E, Lai M, Zhang H. HOTAIRM1 as a potential biomarker for diagnosis of colorectal cancer functions the role in the tumour suppressor. *J Cell Mol Med* 2016; **20**: 2036-2044 [PMID: [27307307](#) DOI: [10.1111/jcmm.12892](#)]
 - 118 **Li Y**, Huang S, Li Y, Zhang W, He K, Zhao M, Lin H, Li D, Zhang H, Zheng Z, Huang C. Decreased expression of lncRNA SLC25A25-AS1 promotes proliferation, chemoresistance, and EMT in colorectal cancer cells. *Tumour Biol* 2016; **37**: 14205-14215 [PMID: [27553025](#) DOI: [10.1007/s13277-016-5254-0](#)]
 - 119 **Ye C**, Shen Z, Wang B, Li Y, Li T, Yang Y, Jiang K, Ye Y, Wang S. A novel long non-coding RNA lnc-GNAT1-1 is low expressed in colorectal cancer and acts as a tumor suppressor through regulating RKIP-NF- κ B-Snail circuit. *J Exp Clin Cancer Res* 2016; **35**: 187 [PMID: [27912775](#) DOI: [10.1186/s13046-016-0467-z](#)]
 - 120 **Li Y**, Li Y, Huang S, He K, Zhao M, Lin H, Li D, Qian J, Zhou C, Chen Y, Huang C. Long non-coding RNA growth arrest specific transcript 5 acts as a tumour suppressor in colorectal cancer by inhibiting interleukin-10 and vascular endothelial growth factor expression. *Oncotarget* 2017; **8**: 13690-13702 [PMID: [28099146](#) DOI: [10.18632/oncotarget.14625](#)]
 - 121 **Cao D**, Ding Q, Yu W, Gao M, Wang Y. Long noncoding RNA SPRY4-IT1 promotes malignant development of colorectal cancer by targeting epithelial-mesenchymal transition. *Onco Targets Ther* 2016; **9**: 5417-5425 [PMID: [27621655](#) DOI: [10.2147/OTT.S111794](#)]
 - 122 **Yue B**, Qiu S, Zhao S, Liu C, Zhang D, Yu F, Peng Z, Yan D. LncRNA-ATB mediated E-cadherin repression promotes the progression of colon cancer and predicts poor prognosis. *J Gastroenterol Hepatol* 2016; **31**: 595-603 [PMID: [26487301](#) DOI: [10.1111/jgh.13206](#)]
 - 123 **Yue B**, Sun B, Liu C, Zhao S, Zhang D, Yu F, Yan D. Long non-coding RNA Fer-1-like protein 4 suppresses oncogenesis and exhibits prognostic value by associating with miR-106a-5p in colon cancer. *Cancer Sci* 2015; **106**: 1323-1332 [PMID: [26224446](#) DOI: [10.1111/cas.12759](#)]
 - 124 **Wang C**, Yu J, Han Y, Li L, Li J, Li T, Qi P. Long non-coding RNAs LOC285194, RP11-462C24.1 and Nbla12061 in serum provide a new approach for distinguishing patients with colorectal cancer from healthy controls. *Oncotarget* 2016; **7**: 70769-70778 [PMID: [27683121](#) DOI: [10.18632/oncotarget.12220](#)]
 - 125 **Wang R**, Du L, Yang X, Jiang X, Duan W, Yan S, Xie Y, Zhu Y, Wang Q, Wang L, Yang Y, Wang C. Identification of long noncoding RNAs as potential novel diagnosis and prognosis biomarkers in colorectal cancer. *J Cancer Res Clin Oncol* 2016; **142**: 2291-2301 [PMID: [27591862](#) DOI: [10.1007/s00432-016-2238-9](#)]
 - 126 **Shi J**, Li X, Zhang F, Zhang C, Guan Q, Cao X, Zhu W, Zhang X, Cheng Y, Ou K, Chen Q, Hu S. Circulating lncRNAs associated with occurrence of colorectal cancer progression. *Am J Cancer Res* 2015; **5**: 2258-2265 [PMID: [26328256](#)]
 - 127 **Xu Y**, Xu Q, Yang L, Ye X, Liu F, Wu F, Ni S, Tan C, Cai G, Meng X, Cai S, Du X. Identification and validation of a blood-based 18-gene expression signature in colorectal cancer. *Clin Cancer Res* 2013; **19**: 3039-3049 [PMID: [23536436](#) DOI: [10.1158/1078-0432.CCR-12-3851](#)]
 - 128 **Wu Y**, Yang L, Zhao J, Li C, Nie J, Liu F, Zhuo C, Zheng Y, Li B, Wang Z, Xu Y. Nuclear-enriched abundant transcript 1 as a diagnostic and prognostic biomarker in colorectal cancer. *Mol Cancer* 2015; **14**: 191 [PMID: [26552600](#) DOI: [10.1186/s12943-015-0455-5](#)]
 - 129 **Dai M**, Chen X, Mo S, Li J, Huang Z, Huang S, Xu J, He B, Zou Y, Chen J, Dai S. Meta-signature lncRNAs serve as novel biomarkers for colorectal cancer: integrated bioinformatics analysis, experimental validation and diagnostic evaluation. *Sci Rep* 2017; **7**: 46572 [PMID: [28406230](#) DOI: [10.1038/srep46572](#)]
 - 130 **Liu H**, Ye D, Chen A, Tan D, Zhang W, Jiang W, Wang M, Zhang X. A pilot study of new promising non-coding RNA diagnostic biomarkers for early-stage colorectal cancers. *Clin Chem Lab Med* 2019; **57**: 1073-1083 [PMID: [30978169](#) DOI: [10.1515/ccbm-2019-0052](#)]
 - 131 **Pedersen SK**, Mitchell SM, Graham LD, McEvoy A, Thomas ML, Baker RT, Ross JP, Xu ZZ, Ho T, LaPointe LC, Young GP, Molloy PL. CAHM, a long non-coding RNA gene hypermethylated in colorectal neoplasia. *Epigenetics* 2014; **9**: 1071-1082 [PMID: [24799664](#) DOI: [10.4161/epi.29046](#)]
 - 132 **Gong W**, Tian M, Qiu H, Yang Z. Elevated serum level of lncRNA-HIF1A-AS1 as a novel diagnostic predictor for worse prognosis in colorectal carcinoma. *Cancer Biomark* 2017; **20**: 417-424 [PMID: [28946548](#) DOI: [10.3233/CBM-170179](#)]
 - 133 **Wang L**, Du L, Duan W, Yan S, Xie Y, Wang C. Overexpression of long noncoding RNA NORAD in colorectal cancer associates with tumor progression. *Onco Targets Ther* 2018; **11**: 6757-6766 [PMID: [30349308](#) DOI: [10.2147/OTT.S176354](#)]
 - 134 **Shaker OG**, Senousy MA, Elbaz EM. Association of rs6983267 at 8q24, HULC rs7763881 polymorphisms and serum lncRNAs CCAT2 and HULC with colorectal cancer in Egyptian patients. *Sci Rep* 2017; **7**: 16246 [PMID: [29176650](#) DOI: [10.1038/s41598-017-16500-4](#)]
 - 135 **Kalluri R**. The biology and function of exosomes in cancer. *J Clin Invest* 2016; **126**: 1208-1215 [PMID: [27035812](#) DOI: [10.1172/JCI81135](#)]
 - 136 **Shao Y**, Shen Y, Chen T, Xu F, Chen X, Zheng S. The functions and clinical applications of tumor-derived exosomes. *Oncotarget* 2016; **7**: 60736-60751 [PMID: [27517627](#) DOI: [10.18632/oncotarget.11177](#)]
 - 137 **Azmi AS**, Bao B, Sarkar FH. Exosomes in cancer development, metastasis, and drug resistance: a comprehensive review. *Cancer Metastasis Rev* 2013; **32**: 623-642 [PMID: [23709120](#) DOI: [10.1007/s10555-013-9441-9](#)]

- 138 **Gao T**, Liu X, He B, Nie Z, Zhu C, Zhang P, Wang S. Exosomal lncRNA 91H is associated with poor development in colorectal cancer by modifying HNRNP expression. *Cancer Cell Int* 2018; **18**: 11 [PMID: 29410604 DOI: 10.1186/s12935-018-0506-2]
- 139 **Hu D**, Zhan Y, Zhu K, Bai M, Han J, Si Y, Zhang H, Kong D. Plasma Exosomal Long Non-Coding RNAs Serve as Biomarkers for Early Detection of Colorectal Cancer. *Cell Physiol Biochem* 2018; **51**: 2704-2715 [PMID: 30562751 DOI: 10.1159/000495961]
- 140 **Dong L**, Lin W, Qi P, Xu MD, Wu X, Ni S, Huang D, Weng WW, Tan C, Sheng W, Zhou X, Du X. Circulating Long RNAs in Serum Extracellular Vesicles: Their Characterization and Potential Application as Biomarkers for Diagnosis of Colorectal Cancer. *Cancer Epidemiol Biomarkers Prev* 2016; **25**: 1158-1166 [PMID: 27197301 DOI: 10.1158/1055-9965.EPI-16-0006]
- 141 **Liu L**, Meng T, Yang XH, Sayim P, Lei C, Jin B, Ge L, Wang HJ. Prognostic and predictive value of long non-coding RNA GAS5 and microRNA-221 in colorectal cancer and their effects on colorectal cancer cell proliferation, migration and invasion. *Cancer Biomark* 2018; **22**: 283-299 [PMID: 29630521 DOI: 10.3233/CBM-171011]
- 142 **Molnár B**, Galamb O, Kalmár A, Barták BK, Nagy ZB, Tóth K, Tulassay Z, Igaz P, Dank M. Circulating cell-free nucleic acids as biomarkers in colorectal cancer screening and diagnosis - an update. *Expert Rev Mol Diagn* 2019; **19**: 477-498 [PMID: 31046485 DOI: 10.1080/14737159.2019.1613891]
- 143 **Ohtsuka M**, Ling H, Ivan C, Pichler M, Matsushita D, Goblirsch M, Stiegelbauer V, Shigeyasu K, Zhang X, Chen M, Vidhu F, Bartholomeusz GA, Toiyama Y, Kusunoki M, Doki Y, Mori M, Song S, Gunther JR, Krishnan S, Slaby O, Goel A, Ajani JA, Radovich M, Calin GA. H19 Noncoding RNA, an Independent Prognostic Factor, Regulates Essential Rb-E2F and CDK8- β -Catenin Signaling in Colorectal Cancer. *EBioMedicine* 2016; **13**: 113-124 [PMID: 27789274 DOI: 10.1016/j.ebiom.2016.10.026]
- 144 **Han D**, Gao X, Wang M, Qiao Y, Xu Y, Yang J, Dong N, He J, Sun Q, Lv G, Xu C, Tao J, Ma N. Long noncoding RNA H19 indicates a poor prognosis of colorectal cancer and promotes tumor growth by recruiting and binding to eIF4A3. *Oncotarget* 2016; **7**: 22159-22173 [PMID: 26989025 DOI: 10.18632/oncotarget.8063]
- 145 **Li Q**, Dai Y, Wang F, Hou S. Differentially expressed long non-coding RNAs and the prognostic potential in colorectal cancer. *Neoplasma* 2016; **63**: 977-983 [PMID: 27596298 DOI: 10.4149/neo_2016_617]
- 146 **Yu B**, Du Q, Li H, Liu HY, Ye X, Zhu B, Zhai Q, Li XX. Diagnostic potential of serum exosomal colorectal neoplasia differentially expressed long non-coding RNA (CRNDE-p) and microRNA-217 expression in colorectal carcinoma. *Oncotarget* 2017; **8**: 83745-83753 [PMID: 29137379 DOI: 10.18632/oncotarget.19407]
- 147 **Li P**, Zhang X, Wang L, Du L, Yang Y, Liu T, Li C, Wang C. lncRNA HOTAIR Contributes to 5FU Resistance through Suppressing miR-218 and Activating NF- κ B/TS Signaling in Colorectal Cancer. *Mol Ther Nucleic Acids* 2017; **8**: 356-369 [PMID: 28918035 DOI: 10.1016/j.omtn.2017.07.007]
- 148 **Xiao Z**, Qu Z, Chen Z, Fang Z, Zhou K, Huang Z, Guo X, Zhang Y. lncRNA HOTAIR is a Prognostic Biomarker for the Proliferation and Chemoresistance of Colorectal Cancer via MiR-203a-3p-Mediated Wnt/ β -Catenin Signaling Pathway. *Cell Physiol Biochem* 2018; **46**: 1275-1285 [PMID: 29680837 DOI: 10.1159/000489110]
- 149 **Li P**, Zhang X, Wang H, Wang L, Liu T, Du L, Yang Y, Wang C. MALAT1 Is Associated with Poor Response to Oxaliplatin-Based Chemotherapy in Colorectal Cancer Patients and Promotes Chemoresistance through EZH2. *Mol Cancer Ther* 2017; **16**: 739-751 [PMID: 28069878 DOI: 10.1158/1535-7163.MCT-16-0591]
- 150 **Ozawa T**, Matsuyama T, Toiyama Y, Takahashi N, Ishikawa T, Uetake H, Yamada Y, Kusunoki M, Calin G, Goel A. CCAT1 and CCAT2 long noncoding RNAs, located within the 8q.24.21 'gene desert', serve as important prognostic biomarkers in colorectal cancer. *Ann Oncol* 2017; **28**: 1882-1888 [PMID: 28838211 DOI: 10.1093/annonc/mdx248]
- 151 **Su J**, Zhang E, Han L, Yin D, Liu Z, He X, Zhang Y, Lin F, Lin Q, Mao P, Mao W, Shen D. Long noncoding RNA BLACAT1 indicates a poor prognosis of colorectal cancer and affects cell proliferation by epigenetically silencing of p15. *Cell Death Dis* 2017; **8**: e2665 [PMID: 28277544 DOI: 10.1038/cddis.2017.83]
- 152 **Deng Q**, He B, Gao T, Pan Y, Sun H, Xu Y, Li R, Ying H, Wang F, Liu X, Chen J, Wang S. Up-regulation of 91H promotes tumor metastasis and predicts poor prognosis for patients with colorectal cancer. *PLoS One* 2014; **9**: e103022 [PMID: 25058480 DOI: 10.1371/journal.pone.0103022]
- 153 **Han X**, Wang L, Ning Y, Li S, Wang Z. Long non-coding RNA AFAP1-AS1 facilitates tumor growth and promotes metastasis in colorectal cancer. *Biol Res* 2016; **49**: 36 [PMID: 27578191 DOI: 10.1186/s40659-016-0094-3]
- 154 **Wang F**, Ni H, Sun F, Li M, Chen L. Overexpression of lncRNA AFAP1-AS1 correlates with poor prognosis and promotes tumorigenesis in colorectal cancer. *Biomed Pharmacother* 2016; **81**: 152-159 [PMID: 27261589 DOI: 10.1016/j.biopha.2016.04.009]
- 155 **Niu H**, Hu Z, Liu H, Hu G, Yang B, Wu S, Li F. Long non-coding RNA AK027294 involves in the process of proliferation, migration, and apoptosis of colorectal cancer cells. *Tumour Biol* 2016; **37**: 10097-10105 [PMID: 26820130 DOI: 10.1007/s13277-015-4350-x]
- 156 **Hu Y**, Chen HY, Yu CY, Xu J, Wang JL, Qian J, Zhang X, Fang JY. A long non-coding RNA signature to improve prognosis prediction of colorectal cancer. *Oncotarget* 2014; **5**: 2230-2242 [PMID: 24809982 DOI: 10.18632/oncotarget.1895]
- 157 **Han J**, Rong LF, Shi CB, Dong XG, Wang J, Wang BL, Wen H, He ZY. Screening of lymph nodes metastasis associated lncRNAs in colorectal cancer patients. *World J Gastroenterol* 2014; **20**: 8139-8150 [PMID: 25009386 DOI: 10.3748/wjg.v20.i25.8139]
- 158 **Sun Y**, Zheng ZP, Li H, Zhang HQ, Ma FQ. ANRIL is associated with the survival rate of patients with colorectal cancer, and affects cell migration and invasion in vitro. *Mol Med Rep* 2016; **14**: 1714-1720 [PMID: 27314206 DOI: 10.3892/mmr.2016.5409]
- 159 **Naemura M**, Tsunoda T, Inoue Y, Okamoto H, Shirasawa S, Kotake Y. ANRIL regulates the proliferation of human colorectal cancer cells in both two- and three-dimensional culture. *Mol Cell Biochem* 2016; **412**: 141-146 [PMID: 26708220 DOI: 10.1007/s11010-015-2618-5]
- 160 **Iguchi T**, Uchi R, Nambara S, Saito T, Komatsu H, Hirata H, Ueda M, Sakimura S, Takano Y, Kurashige J, Shinden Y, Eguchi H, Sugimachi K, Maehara Y, Mimori K. A long noncoding RNA, lncRNA-ATB, is involved in the progression and prognosis of colorectal cancer. *Anticancer Res* 2015; **35**: 1385-1388 [PMID: 25750289]
- 161 **Li W**, Kang Y. A new lnc in metastasis: long noncoding RNA mediates the prometastatic functions of TGF- β . *Cancer Cell* 2014; **25**: 557-559 [PMID: 24823634 DOI: 10.1016/j.ccr.2014.04.014]

- 162 **Davison EJ**, Tarpey PS, Fiegler H, Tomlinson IP, Carter NP. Deletion at chromosome band 20p12.1 in colorectal cancer revealed by high resolution array comparative genomic hybridization. *Genes Chromosomes Cancer* 2005; **44**: 384-391 [PMID: [16110499](#) DOI: [10.1002/gcc.20252](#)]
- 163 **Shi Y**, Liu Y, Wang J, Jie D, Yun T, Li W, Yan L, Wang K, Feng J. Downregulated Long Noncoding RNA BANCR Promotes the Proliferation of Colorectal Cancer Cells via Downregulation of p21 Expression. *PLoS One* 2015; **10**: e0122679 [PMID: [25928067](#) DOI: [10.1371/journal.pone.0122679](#)]
- 164 **Guo Q**, Zhao Y, Chen J, Hu J, Wang S, Zhang D, Sun Y. BRAF-activated long non-coding RNA contributes to colorectal cancer migration by inducing epithelial-mesenchymal transition. *Oncol Lett* 2014; **8**: 869-875 [PMID: [25013510](#) DOI: [10.3892/ol.2014.2154](#)]
- 165 **Gao X**, Wen J, Gao P, Zhang G, Zhang G. Overexpression of the long non-coding RNA, linc-UBC1, is associated with poor prognosis and facilitates cell proliferation, migration, and invasion in colorectal cancer. *Onco Targets Ther* 2017; **10**: 1017-1026 [PMID: [28260919](#) DOI: [10.2147/OTT.S129343](#)]
- 166 **Zhang Z**, Zhou C, Chang Y, Zhang Z, Hu Y, Zhang F, Lu Y, Zheng L, Zhang W, Li X, Li X. Long non-coding RNA CASC11 interacts with hnRNP-K and activates the WNT/ β -catenin pathway to promote growth and metastasis in colorectal cancer. *Cancer Lett* 2016; **376**: 62-73 [PMID: [27012187](#) DOI: [10.1016/j.canlet.2016.03.022](#)]
- 167 **Huang G**, Wu X, Li S, Xu X, Zhu H, Chen X. The long noncoding RNA CASC2 functions as a competing endogenous RNA by sponging miR-18a in colorectal cancer. *Sci Rep* 2016; **6**: 26524 [PMID: [27198161](#) DOI: [10.1038/srep26524](#)]
- 168 **Xin Y**, Li Z, Shen J, Chan MT, Wu WK. CCAT1: a pivotal oncogenic long non-coding RNA in human cancers. *Cell Prolif* 2016; **49**: 255-260 [PMID: [27134049](#) DOI: [10.1111/cpr.12252](#)]
- 169 **McClelland ML**, Mesh K, Lorenzana E, Chopra VS, Segal E, Watanabe C, Haley B, Mayba O, Yaylaoglu M, Gnad F, Firestein R. CCAT1 is an enhancer-templated RNA that predicts BET sensitivity in colorectal cancer. *J Clin Invest* 2016; **126**: 639-652 [PMID: [26752646](#) DOI: [10.1172/JCI83265](#)]
- 170 **Ye Z**, Zhou M, Tian B, Wu B, Li J. Expression of lncRNA-CCAT1, E-cadherin and N-cadherin in colorectal cancer and its clinical significance. *Int J Clin Exp Med* 2015; **8**: 3707-3715 [PMID: [26064266](#)]
- 171 **Xiang JF**, Yin QF, Chen T, Zhang Y, Zhang XO, Wu Z, Zhang S, Wang HB, Ge J, Lu X, Yang L, Chen LL. Human colorectal cancer-specific CCAT1-L lncRNA regulates long-range chromatin interactions at the MYC locus. *Cell Res* 2014; **24**: 513-531 [PMID: [24662484](#) DOI: [10.1038/cr.2014.35](#)]
- 172 **Ling H**, Spizzo R, Atlasi Y, Nicoloso M, Shimizu M, Redis RS, Nishida N, Gafà R, Song J, Guo Z, Ivan C, Barbarotto E, De Vries I, Zhang X, Ferracin M, Churchman M, van Galen JF, Beverloo BH, Shariati M, Haderk F, Estecio MR, Garcia-Manero G, Patijn GA, Gotley DC, Bhardwaj V, Shureiqi I, Sen S, Multani AS, Welsh J, Yamamoto K, Taniguchi I, Song MA, Gallinger S, Casey G, Thibodeau SN, Le Marchand L, Tiirikainen M, Mani SA, Zhang W, Davuluri RV, Mimori K, Mori M, Sieuwerts AM, Martens JW, Tomlinson I, Negrini M, Berindan-Neagoe I, Foekens JA, Hamilton SR, Lanza G, Kopetz S, Fodde R, Calin GA. CCAT2, a novel noncoding RNA mapping to 8q24, underlies metastatic progression and chromosomal instability in colon cancer. *Genome Res* 2013; **23**: 1446-1461 [PMID: [23796952](#) DOI: [10.1101/gr.152942.112](#)]
- 173 **Kasagi Y**, Oki E, Ando K, Ito S, Iguchi T, Sugiyama M, Nakashima Y, Ohgaki K, Saeki H, Mimori K, Maehara Y. The Expression of CCAT2, a Novel Long Noncoding RNA Transcript, and rs6983267 Single-Nucleotide Polymorphism Genotypes in Colorectal Cancers. *Oncology* 2017; **92**: 48-54 [PMID: [27875818](#) DOI: [10.1159/000452143](#)]
- 174 **Ye LC**, Ren L, Qiu JJ, Zhu DX, Chen T, Chang WJ, Lv SX, Xu J. Aberrant expression of long noncoding RNAs in colorectal cancer with liver metastasis. *Tumour Biol* 2015; **36**: 8747-8754 [PMID: [26050227](#) DOI: [10.1007/s13277-015-3627-4](#)]
- 175 **Ye LC**, Chen T, Zhu DX, Lv SX, Qiu JJ, Xu J, Yuan FL, Wei Y. Downregulated long non-coding RNA CLMAT3 promotes the proliferation of colorectal cancer cells by targeting regulators of the cell cycle pathway. *Oncotarget* 2016; **7**: 58931-58938 [PMID: [27391344](#) DOI: [10.18632/oncotarget.10431](#)]
- 176 **Yuan Z**, Yu X, Ni B, Chen D, Yang Z, Huang J, Wang J, Chen D, Wang L. Overexpression of long non-coding RNA-CTD903 inhibits colorectal cancer invasion and migration by repressing Wnt/ β -catenin signaling and predicts favorable prognosis. *Int J Oncol* 2016; **48**: 2675-2685 [PMID: [27035092](#) DOI: [10.3892/ijo.2016.3447](#)]
- 177 **Chen X**, Zhu H, Wu X, Xie X, Huang G, Xu X, Li S, Xing C. Downregulated pseudogene CTNNAP1 promote tumor growth in human cancer by downregulating its cognate gene CTNNA1 expression. *Oncotarget* 2016; **7**: 55518-55528 [PMID: [27487124](#) DOI: [10.18632/oncotarget.10833](#)]
- 178 **Liu Y**, Zhang M, Liang L, Li J, Chen YX. Over-expression of lncRNA DANCR is associated with advanced tumor progression and poor prognosis in patients with colorectal cancer. *Int J Clin Exp Pathol* 2015; **8**: 11480-11484 [PMID: [26617879](#)]
- 179 **Sun L**, Xue H, Jiang C, Zhou H, Gu L, Liu Y, Xu C, Xu Q. LncRNA DQ786243 contributes to proliferation and metastasis of colorectal cancer both in vitro and in vivo. *Biosci Rep* 2016; **36** [PMID: [26934980](#) DOI: [10.1042/bsr20160048](#)]
- 180 **Yochum GS**, Cleland R, McWeeney S, Goodman RH. An antisense transcript induced by Wnt/ β -catenin signaling decreases E2F4. *J Biol Chem* 2007; **282**: 871-878 [PMID: [17121828](#) DOI: [10.1074/jbc.M609391200](#)]
- 181 **Yang P**, Xu ZP, Chen T, He ZY. Long noncoding RNA expression profile analysis of colorectal cancer and metastatic lymph node based on microarray data. *Onco Targets Ther* 2016; **9**: 2465-2478 [PMID: [27217770](#) DOI: [10.2147/OTT.S102348](#)]
- 182 **Chen N**, Guo D, Xu Q, Yang M, Wang D, Peng M, Ding Y, Wang S, Zhou J. Long non-coding RNA FEZF1-AS1 facilitates cell proliferation and migration in colorectal carcinoma. *Oncotarget* 2016; **7**: 11271-11283 [PMID: [26848625](#) DOI: [10.18632/oncotarget.7168](#)]
- 183 **Guo XB**, Hua Z, Li C, Peng LP, Wang JS, Wang B, Zhi QM. Biological significance of long non-coding RNA FTX expression in human colorectal cancer. *Int J Clin Exp Med* 2015; **8**: 15591-15600 [PMID: [26629053](#)]
- 184 **Yang P**, Chen T, Xu Z, Zhu H, Wang J, He Z. Long noncoding RNA GAPLINC promotes invasion in colorectal cancer by targeting SNAI2 through binding with PSF and NONO. *Oncotarget* 2016; **7**: 42183-42194 [PMID: [27259250](#) DOI: [10.18632/oncotarget.9741](#)]
- 185 **Yin D**, He X, Zhang E, Kong R, De W, Zhang Z. Long noncoding RNA GAS5 affects cell proliferation and predicts a poor prognosis in patients with colorectal cancer. *Med Oncol* 2014; **31**: 253 [PMID: [25326054](#) DOI: [10.1007/s12032-014-0253-8](#)]
- 186 **Ma C**, Shi X, Zhu Q, Li Q, Liu Y, Yao Y, Song Y. The growth arrest-specific transcript 5 (GAS5): a pivotal tumor suppressor long noncoding RNA in human cancers. *Tumour Biol* 2016; **37**: 1437-1444

- [PMID: 26634743 DOI: 10.1007/s13277-015-4521-9]
- 187 **Krell J**, Frampton AE, Mirnezami R, Harding V, De Giorgio A, Roca Alonso L, Cohen P, Ottaviani S, Colombo T, Jacob J, Pellegrino L, Buchanan G, Stebbing J, Castellano L. Growth arrest-specific transcript 5 associated snoRNA levels are related to p53 expression and DNA damage in colorectal cancer. *PLoS One* 2014; **9**: e98561 [PMID: 24926850 DOI: 10.1371/journal.pone.0098561]
 - 188 **Zheng Y**, Song D, Xiao K, Yang C, Ding Y, Deng W, Tong S. LncRNA GAS5 contributes to lymphatic metastasis in colorectal cancer. *Oncotarget* 2016; **7**: 83727-83734 [PMID: 27863421 DOI: 10.18632/oncotarget.13384]
 - 189 **Zhou J**, Li X, Wu M, Lin C, Guo Y, Tian B. Knockdown of Long Noncoding RNA GHET1 Inhibits Cell Proliferation and Invasion of Colorectal Cancer. *Oncol Res* 2016; **23**: 303-309 [PMID: 27131316]
 - 190 **Liang WC**, Fu WM, Wong CW, Wang Y, Wang WM, Hu GX, Zhang L, Xiao LJ, Wan DC, Zhang JF, Waye MM. The lncRNA H19 promotes epithelial to mesenchymal transition by functioning as miRNA sponges in colorectal cancer. *Oncotarget* 2015; **6**: 22513-22525 [PMID: 26068968 DOI: 10.18632/oncotarget.4154]
 - 191 **Wu KF**, Liang WC, Feng L, Pang JX, Waye MM, Zhang JF, Fu WM. H19 mediates methotrexate resistance in colorectal cancer through activating Wnt/ β -catenin pathway. *Exp Cell Res* 2017; **350**: 312-317 [PMID: 27919747 DOI: 10.1016/j.yexcr.2016.12.003]
 - 192 **Yao J**, Li J, Geng P, Li Y, Chen H, Zhu Y. Knockdown of a HIF-2 α promoter upstream long noncoding RNA impairs colorectal cancer stem cell properties in vitro through HIF-2 α downregulation. *Onco Targets Ther* 2015; **8**: 3467-3474 [PMID: 26648739 DOI: 10.2147/OTT.S81393]
 - 193 **Dou J**, Ni Y, He X, Wu D, Li M, Wu S, Zhang R, Guo M, Zhao F. Decreasing lncRNA HOTAIR expression inhibits human colorectal cancer stem cells. *Am J Transl Res* 2016; **8**: 98-108 [PMID: 27069543]
 - 194 **Luo ZF**, Zhao D, Li XQ, Cui YX, Ma N, Lu CX, Liu MY, Zhou Y. Clinical significance of HOTAIR expression in colon cancer. *World J Gastroenterol* 2016; **22**: 5254-5259 [PMID: 27298568 DOI: 10.3748/wjg.v22.i22.5254]
 - 195 **Ren YK**, Xiao Y, Wan XB, Zhao YZ, Li J, Li Y, Han GS, Chen XB, Zou QY, Wang GC, Lu CM, Xu YC, Wang YC. Association of long non-coding RNA HOTTIP with progression and prognosis in colorectal cancer. *Int J Clin Exp Pathol* 2015; **8**: 11458-11463 [PMID: 26617875]
 - 196 **Lian Y**, Ding J, Zhang Z, Shi Y, Zhu Y, Li J, Peng P, Wang J, Fan Y, De W, Wang K. The long noncoding RNA HOXA transcript at the distal tip promotes colorectal cancer growth partially via silencing of p21 expression. *Tumour Biol* 2016; **37**: 7431-7440 [PMID: 26678886 DOI: 10.1007/s13277-015-4617-2]
 - 197 **Yang XJ**, Huang CQ, Peng CW, Hou JX, Liu JY. Long noncoding RNA HULC promotes colorectal carcinoma progression through epigenetically repressing NKD2 expression. *Gene* 2016; **592**: 172-178 [PMID: 27496341 DOI: 10.1016/j.gene.2016.08.002]
 - 198 **Tanaka K**, Shiota G, Meguro M, Mitsuya K, Oshimura M, Kawasaki H. Loss of imprinting of long QT intronic transcript 1 in colorectal cancer. *Oncology* 2001; **60**: 268-273 [PMID: 11340379 DOI: 10.1159/000055328]
 - 199 **Nakano S**, Murakami K, Meguro M, Soejima H, Higashimoto K, Urano T, Kugoh H, Mukai T, Ikeguchi M, Oshimura M. Expression profile of LIT1/KCNQ1OT1 and epigenetic status at the KvDMR1 in colorectal cancers. *Cancer Sci* 2006; **97**: 1147-1154 [PMID: 16965397 DOI: 10.1111/j.1349-7006.2006.00305.x]
 - 200 **Kong J**, Sun W, Li C, Wan L, Wang S, Wu Y, Xu E, Zhang H, Lai M. Long non-coding RNA LINC01133 inhibits epithelial-mesenchymal transition and metastasis in colorectal cancer by interacting with SRSF6. *Cancer Lett* 2016; **380**: 476-484 [PMID: 27443606 DOI: 10.1016/j.canlet.2016.07.015]
 - 201 **Qiu JJ**, Yan JB. Long non-coding RNA LINC01296 is a potential prognostic biomarker in patients with colorectal cancer. *Tumour Biol* 2015; **36**: 7175-7183 [PMID: 25894381 DOI: 10.1007/s13277-015-3448-5]
 - 202 **Zhai H**, Fesler A, Schee K, Fodstad O, Flatmark K, Ju J. Clinical significance of long intergenic noncoding RNA-p21 in colorectal cancer. *Clin Colorectal Cancer* 2013; **12**: 261-266 [PMID: 24012455 DOI: 10.1016/j.clcc.2013.06.003]
 - 203 **Wang J**, Lei ZJ, Guo Y, Wang T, Qin ZY, Xiao HL, Fan LL, Chen DF, Bian XW, Liu J, Wang B. miRNA-regulated delivery of lincRNA-p21 suppresses β -catenin signaling and tumorigenicity of colorectal cancer stem cells. *Oncotarget* 2015; **6**: 37852-37870 [PMID: 26497997 DOI: 10.18632/oncotarget.5635]
 - 204 **Wang G**, Li Z, Zhao Q, Zhu Y, Zhao C, Li X, Ma Z, Li X, Zhang Y. LincRNA-p21 enhances the sensitivity of radiotherapy for human colorectal cancer by targeting the Wnt/ β -catenin signaling pathway. *Oncol Rep* 2014; **31**: 1839-1845 [PMID: 24573322 DOI: 10.3892/or.2014.3047]
 - 205 **Wang L**, Bu P, Ai Y, Srinivasan T, Chen HJ, Xiang K, Lipkin SM, Shen X. A long non-coding RNA targets microRNA miR-34a to regulate colon cancer stem cell asymmetric division. *Elife* 2016; **5** [PMID: 27077950 DOI: 10.7554/eLife.14620]
 - 206 **Yang F**, Huo XS, Yuan SX, Zhang L, Zhou WP, Wang F, Sun SH. Repression of the long noncoding RNA-LET by histone deacetylase 3 contributes to hypoxia-mediated metastasis. *Mol Cell* 2013; **49**: 1083-1096 [PMID: 23395002 DOI: 10.1016/j.molcel.2013.01.010]
 - 207 **Kazemzadeh M**, Safaralizadeh R, Feizi MA, Ravanbakhsh R, Somi MH, Hashemzadeh S. LOC100287225, novel long intergenic non-coding RNA, misregulates in colorectal cancer. *Cancer Biomark* 2016; **16**: 499-505 [PMID: 27062707 DOI: 10.3233/CBM-160589]
 - 208 **Kazemzadeh M**, Safaralizadeh R, Feizi MA, Somi MH, Shokooli B. Misregulation of the dependence receptor DCC and its upstream lincRNA, LOC100287225, in colorectal cancer. *Tumori* 2017; **103**: 40-43 [PMID: 26429648 DOI: 10.5301/tj.5000426]
 - 209 **Qi P**, Xu MD, Ni SJ, Huang D, Wei P, Tan C, Zhou XY, Du X. Low expression of LOC285194 is associated with poor prognosis in colorectal cancer. *J Transl Med* 2013; **11**: 122 [PMID: 23680400 DOI: 10.1186/1479-5876-11-122]
 - 210 **Xu J**, Zhang R, Zhao J. The Novel Long Noncoding RNA TUSC7 Inhibits Proliferation by Sponging MiR-211 in Colorectal Cancer. *Cell Physiol Biochem* 2017; **41**: 635-644 [PMID: 28214867 DOI: 10.1159/000457938]
 - 211 **Ding J**, Lu B, Wang J, Wang J, Shi Y, Lian Y, Zhu Y, Wang J, Fan Y, Wang Z, De W, Wang K. Long non-coding RNA Loc554202 induces apoptosis in colorectal cancer cells via the caspase cleavage cascades. *J Exp Clin Cancer Res* 2015; **34**: 100 [PMID: 26362196 DOI: 10.1186/s13046-015-0217-7]
 - 212 **Yang L**, Wei H, Xiao HJ. Long non-coding RNA Loc554202 expression as a prognostic factor in patients with colorectal cancer. *Eur Rev Med Pharmacol Sci* 2016; **20**: 4243-4247 [PMID: 27831651]

- 213 **Yang MH**, Hu ZY, Xu C, Xie LY, Wang XY, Chen SY, Li ZG. MALAT1 promotes colorectal cancer cell proliferation/migration/invasion via PRKA kinase anchor protein 9. *Biochim Biophys Acta* 2015; **1852**: 166-174 [PMID: [25446987](#) DOI: [10.1016/j.bbdis.2014.11.013](#)]
- 214 **Wang Y**, Xue D, Li Y, Pan X, Zhang X, Kuang B, Zhou M, Li X, Xiong W, Li G, Zeng Z, Yang T. The Long Noncoding RNA MALAT-1 is A Novel Biomarker in Various Cancers: A Meta-analysis Based on the GEO Database and Literature. *J Cancer* 2016; **7**: 991-1001 [PMID: [27313790](#) DOI: [10.7150/jca.14663](#)]
- 215 **Li L**, Shang J, Zhang Y, Liu S, Peng Y, Zhou Z, Pan H, Wang X, Chen L, Zhao Q. MEG3 is a prognostic factor for CRC and promotes chemosensitivity by enhancing oxaliplatin-induced cell apoptosis. *Oncol Rep* 2017; **38**: 1383-1392 [PMID: [28731151](#) DOI: [10.3892/or.2017.5828](#)]
- 216 **Yin DD**, Liu ZJ, Zhang E, Kong R, Zhang ZH, Guo RH. Decreased expression of long noncoding RNA MEG3 affects cell proliferation and predicts a poor prognosis in patients with colorectal cancer. *Tumour Biol* 2015; **36**: 4851-4859 [PMID: [25636452](#) DOI: [10.1007/s13277-015-3139-2](#)]
- 217 **Kong H**, Wu Y, Zhu M, Zhai C, Qian J, Gao X, Wang S, Hou Y, Lu S, Zhu H. Long non-coding RNAs: novel prognostic biomarkers for liver metastases in patients with early stage colorectal cancer. *Oncotarget* 2016; **7**: 50428-50436 [PMID: [27391432](#) DOI: [10.18632/oncotarget.10416](#)]
- 218 **Cao X**, Zhuang S, Hu Y, Xi L, Deng L, Sheng H, Shen W. Associations between polymorphisms of long non-coding RNA MEG3 and risk of colorectal cancer in Chinese. *Oncotarget* 2016; **7**: 19054-19059 [PMID: [26934323](#) DOI: [10.18632/oncotarget.7764](#)]
- 219 **Franklin JL**, Rankin CR, Levy S, Snoddy JR, Zhang B, Washington MK, Thomson JM, Whitehead RH, Coffey RJ. Malignant transformation of colonic epithelial cells by a colon-derived long noncoding RNA. *Biochem Biophys Res Commun* 2013; **440**: 99-104 [PMID: [24045012](#) DOI: [10.1016/j.bbrc.2013.09.040](#)]
- 220 **Qi P**, Xu MD, Ni SJ, Shen XH, Wei P, Huang D, Tan C, Sheng WQ, Zhou XY, Du X. Down-regulation of ncRAN, a long non-coding RNA, contributes to colorectal cancer cell migration and invasion and predicts poor overall survival for colorectal cancer patients. *Mol Carcinog* 2015; **54**: 742-750 [PMID: [24519959](#) DOI: [10.1002/mc.22137](#)]
- 221 **Smolle M**, Uranitsch S, Gerger A, Pichler M, Haybaeck J. Current status of long non-coding RNAs in human cancer with specific focus on colorectal cancer. *Int J Mol Sci* 2014; **15**: 13993-14013 [PMID: [25119862](#) DOI: [10.3390/ijms150813993](#)]
- 222 **Yan B**, Gu W, Yang Z, Gu Z, Yue X, Gu Q, Liu L. Downregulation of a long noncoding RNA-ncRUPAR contributes to tumor inhibition in colorectal cancer. *Tumour Biol* 2014; **35**: 11329-11335 [PMID: [25119598](#) DOI: [10.1007/s13277-014-2465-0](#)]
- 223 **Li Y**, Li Y, Chen W, He F, Tan Z, Zheng J, Wang W, Zhao Q, Li J. NEAT expression is associated with tumor recurrence and unfavorable prognosis in colorectal cancer. *Oncotarget* 2015; **6**: 27641-27650 [PMID: [26314847](#) DOI: [10.18632/oncotarget.4737](#)]
- 224 **Lu M**, Liu Z, Li B, Wang G, Li D, Zhu Y. The high expression of long non-coding RNA PANDAR indicates a poor prognosis for colorectal cancer and promotes metastasis by EMT pathway. *J Cancer Res Clin Oncol* 2017; **143**: 71-81 [PMID: [27629879](#) DOI: [10.1007/s00432-016-2252-y](#)]
- 225 **Ge X**, Chen Y, Liao X, Liu D, Li F, Ruan H, Jia W. Overexpression of long noncoding RNA PCAT-1 is a novel biomarker of poor prognosis in patients with colorectal cancer. *Med Oncol* 2013; **30**: 588 [PMID: [23640607](#) DOI: [10.1007/s12032-013-0588-6](#)]
- 226 **Yang L**, Qiu M, Xu Y, Wang J, Zheng Y, Li M, Xu L, Yin R. Upregulation of long non-coding RNA PRNCR1 in colorectal cancer promotes cell proliferation and cell cycle progression. *Oncol Rep* 2016; **35**: 318-324 [PMID: [26530130](#) DOI: [10.3892/or.2015.4364](#)]
- 227 **Li L**, Sun R, Liang Y, Pan X, Li Z, Bai P, Zeng X, Zhang D, Zhang L, Gao L. Association between polymorphisms in long non-coding RNA PRNCR1 in 8q24 and risk of colorectal cancer. *J Exp Clin Cancer Res* 2013; **32**: 104 [PMID: [24330491](#) DOI: [10.1186/1756-9966-32-104](#)]
- 228 **Takahashi Y**, Sawada G, Kurashige J, Uchi R, Matsumura T, Ueo H, Takano Y, Eguchi H, Sudo T, Sugimachi K, Yamamoto H, Doki Y, Mori M, Mimori K. Amplification of PVT-1 is involved in poor prognosis via apoptosis inhibition in colorectal cancers. *Br J Cancer* 2014; **110**: 164-171 [PMID: [24196785](#) DOI: [10.1038/bjc.2013.698](#)]
- 229 **Liu J**, Wang J, Song Y, Yang Y, Hu Y, Gao P, Sun J, Chen X, Xu Y, Wang Z. A potential biomarker for colorectal cancer: long non-coding RNA RPI-13P20.6. *Neoplasma* 2016; **63**: 984-990 [PMID: [27596299](#) DOI: [10.4149/neo_2016_618](#)]
- 230 **Chen H**, Xu J, Hong J, Tang R, Zhang X, Fang JY. Long noncoding RNA profiles identify five distinct molecular subtypes of colorectal cancer with clinical relevance. *Mol Oncol* 2014; **8**: 1393-1403 [PMID: [24954858](#) DOI: [10.1016/j.molonc.2014.05.010](#)]
- 231 **Shi D**, Zheng H, Zhuo C, Peng J, Li D, Xu Y, Li X, Cai G, Cai S. Low expression of novel lncRNA RP11-462C24.1 suggests a biomarker of poor prognosis in colorectal cancer. *Med Oncol* 2014; **31**: 31 [PMID: [24908062](#) DOI: [10.1007/s12032-014-0031-7](#)]
- 232 **Lee H**, Kim C, Ku JL, Kim W, Yoon SK, Kuh HJ, Lee JH, Nam SW, Lee EK. A long non-coding RNA snR contributes to 5-fluorouracil resistance in human colon cancer cells. *Mol Cells* 2014; **37**: 540-546 [PMID: [25078450](#) DOI: [10.14348/molcells.2014.0151](#)]
- 233 **Li C**, Zhou L, He J, Fang XQ, Zhu SW, Xiong MM. Increased long noncoding RNA SNHG20 predicts poor prognosis in colorectal cancer. *BMC Cancer* 2016; **16**: 655 [PMID: [27543107](#) DOI: [10.1186/s12885-016-2719-x](#)]
- 234 **Wang JZ**, Xu CL, Wu H, Shen SJ. LncRNA SNHG12 promotes cell growth and inhibits cell apoptosis in colorectal cancer cells. *Braz J Med Biol Res* 2017; **50**: e6079 [PMID: [28225893](#) DOI: [10.1590/1414-431X20176079](#)]
- 235 **Liu S**, Xu B, Yan D. Enhanced expression of long non-coding RNA Sox2ot promoted cell proliferation and motility in colorectal cancer. *Minerva Med* 2016; **107**: 279-286 [PMID: [27353770](#)]
- 236 **Shen F**, Cai WS, Feng Z, Chen JW, Feng JH, Liu QC, Fang YP, Li KP, Xiao HQ, Cao J, Xu B. Long non-coding RNA SPRY4-IT1 promotes colorectal cancer metastasis by regulate epithelial-mesenchymal transition. *Oncotarget* 2017; **8**: 14479-14486 [PMID: [27391336](#) DOI: [10.18632/oncotarget.10407](#)]
- 237 **Zhang ZY**, Lu YX, Zhang ZY, Chang YY, Zheng L, Yuan L, Zhang F, Hu YH, Zhang WJ, Li XN. Loss of TINCR expression promotes proliferation, metastasis through activating EpCAM cleavage in colorectal cancer. *Oncotarget* 2016; **7**: 22639-22649 [PMID: [27009809](#) DOI: [10.18632/oncotarget.8141](#)]
- 238 **Sun J**, Ding C, Yang Z, Liu T, Zhang X, Zhao C, Wang J. The long non-coding RNA TUG1 indicates a poor prognosis for colorectal cancer and promotes metastasis by affecting epithelial-mesenchymal transition. *J Transl Med* 2016; **14**: 42 [PMID: [26856330](#) DOI: [10.1186/s12967-016-0786-z](#)]
- 239 **Wang L**, Zhao Z, Feng W, Ye Z, Dai W, Zhang C, Peng J, Wu K. Long non-coding RNA TUG1 promotes

- colorectal cancer metastasis via EMT pathway. *Oncotarget* 2016; **7**: 51713-51719 [PMID: [27421138](#) DOI: [10.18632/oncotarget.10563](#)]
- 240 **Zhai HY**, Sui MH, Yu X, Qu Z, Hu JC, Sun HQ, Zheng HT, Zhou K, Jiang LX. Overexpression of Long Non-Coding RNA TUG1 Promotes Colon Cancer Progression. *Med Sci Monit* 2016; **22**: 3281-3287 [PMID: [27634385](#)]
 - 241 **Sana J**, Hankeova S, Svoboda M, Kiss I, Vyzula R, Slaby O. Expression levels of transcribed ultraconserved regions uc.73 and uc.388 are altered in colorectal cancer. *Oncology* 2012; **82**: 114-118 [PMID: [22328099](#) DOI: [10.1159/000336479](#)]
 - 242 **Calin GA**, Liu CG, Ferracin M, Hyslop T, Spizzo R, Sevignani C, Fabbri M, Cimmino A, Lee EJ, Wojcik SE, Shimizu M, Tili E, Rossi S, Taccioli C, Pichiorri F, Liu X, Zupo S, Herlea V, Gramantieri L, Lanza G, Alder H, Rassenti L, Volinia S, Schmittgen TD, Kipps TJ, Negrini M, Croce CM. Ultraconserved regions encoding ncRNAs are altered in human leukemias and carcinomas. *Cancer Cell* 2007; **12**: 215-229 [PMID: [17785203](#) DOI: [10.1016/j.ccr.2007.07.027](#)]
 - 243 **Wu X**, He X, Li S, Xu X, Chen X, Zhu H. Long Non-Coding RNA uc002kmd.1 Regulates CD44-Dependent Cell Growth by Competing for miR-211-3p in Colorectal Cancer. *PLoS One* 2016; **11**: e0151287 [PMID: [26974151](#) DOI: [10.1371/journal.pone.0151287](#)]
 - 244 **Bian Z**, Jin L, Zhang J, Yin Y, Quan C, Hu Y, Feng Y, Liu H, Fei B, Mao Y, Zhou L, Qi X, Huang S, Hua D, Xing C, Huang Z. LncRNA-UCA1 enhances cell proliferation and 5-fluorouracil resistance in colorectal cancer by inhibiting miR-204-5p. *Sci Rep* 2016; **6**: 23892 [PMID: [27046651](#) DOI: [10.1038/srep23892](#)]
 - 245 **Ni B**, Yu X, Guo X, Fan X, Yang Z, Wu P, Yuan Z, Deng Y, Wang J, Chen D, Wang L. Increased urothelial cancer associated 1 is associated with tumor proliferation and metastasis and predicts poor prognosis in colorectal cancer. *Int J Oncol* 2015; **47**: 1329-1338 [PMID: [26238511](#) DOI: [10.3892/ijo.2015.3109](#)]
 - 246 **Taniue K**, Kurimoto A, Sugimasa H, Nasu E, Takeda Y, Iwasaki K, Nagashima T, Okada-Hatakeyama M, Oyama M, Kozuka-Hata H, Hiyoshi M, Kitayama J, Negishi L, Kawasaki Y, Akiyama T. Long noncoding RNA UPAT promotes colon tumorigenesis by inhibiting degradation of UHRF1. *Proc Natl Acad Sci USA* 2016; **113**: 1273-1278 [PMID: [26768845](#) DOI: [10.1073/pnas.1500992113](#)]
 - 247 **Lassmann S**, Weis R, Makowiec F, Roth J, Danciu M, Hopt U, Werner M. Array CGH identifies distinct DNA copy number profiles of oncogenes and tumor suppressor genes in chromosomal- and microsatellite-unstable sporadic colorectal carcinomas. *J Mol Med (Berl)* 2007; **85**: 293-304 [PMID: [17143621](#) DOI: [10.1007/s00109-006-0126-5](#)]
 - 248 **Xiao Y**, Yurievich UA, Yosypovych SV. Long noncoding RNA XIST is a prognostic factor in colorectal cancer and inhibits 5-fluorouracil-induced cell cytotoxicity through promoting thymidylate synthase expression. *Oncotarget* 2017; **8**: 83171-83182 [PMID: [29137332](#) DOI: [10.18632/oncotarget.20487](#)]
 - 249 **Wang W**, Xing C. Upregulation of long noncoding RNA ZFAS1 predicts poor prognosis and prompts invasion and metastasis in colorectal cancer. *Pathol Res Pract* 2016; **212**: 690-695 [PMID: [27461828](#) DOI: [10.1016/j.prp.2016.05.003](#)]
 - 250 **Kumegawa K**, Maruyama R, Yamamoto E, Ashida M, Kitajima H, Tsuyada A, Niinuma T, Kai M, Yamano HO, Sugai T, Tokino T, Shinomura Y, Imai K, Suzuki H. A genomic screen for long noncoding RNA genes epigenetically silenced by aberrant DNA methylation in colorectal cancer. *Sci Rep* 2016; **6**: 26699 [PMID: [27215978](#) DOI: [10.1038/srep26699](#)]



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