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REVIEW



Noncoding RNAs in inflammation and colorectal cancer

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ABSTRACT

Despite advanced clinical treatments, mortality in patients with metastatic colorectal cancer (CRC) remains high. Three critical determinants in CRC progression include the epithelial proliferation checkpoints, epithelial-to-mesenchymal transition (EMT) and inflammatory cytokines in the tumour microenvironment. Genes involved in these three processes are regulated at the transcriptional and post-transcriptional level. Recent studies revealed previously unappreciated roles of non-coding ribonucleic acids (ncRNAs) in modulating the proliferation checkpoints, EMT, and inflammatory gene expression in CRC. In this review, we will discuss the mechanisms underlying the roles of ncRNAs in CRC as well as examine future perspectives in this field. Better understanding of ncRNA biology will provide novel targets for future therapeutic development.

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Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide. Each year, there are over 100,000 newly diagnosed cases and greater than 50,000 related mortalities in the U.S. alone [1]. CRC is an adenocarcinoma originating from the epithelial cancer stem cells of the colon or rectum with pluripotency and self-renewal capabilities [2]. CRC initiation is characterized by the acquisition of genetic mutations in common signalling pathways, such as the wingless-type MMTV integration site (*Wnt*) and the transforming growth factor-beta (TGF β) pathways, allowing for the bypass of cell cycle checkpoints [3–5]. Subsequent activation of the epithelial-to-mesenchymal transition (EMT) program is a critical step towards progression to invasive cancer and metastasis [6], which is a major cause of CRC-related mortality.

Recent high-throughput genomics efforts have identified a vast number of non-coding RNAs (ncRNAs) aberrantly expressed in CRC, fuelling a growing appreciation for their diverse roles in CRC initiation, growth and metastasis [7,8]. ncRNAs consist of two subgroups based on RNA length: the small non-coding RNAs (sncRNAs; less than 200 nucleotides) and the long-noncoding RNAs (lncRNAs; greater than 200 nucleotides). microRNAs (miRNAs) of the sncRNA family and diverse members of the lncRNA family are well studied in CRC and therefore form the major focus of this review.

General mechanisms underlying ncRNAs regulations of gene expression

sncRNAs and lncRNAs can form unique secondary and/or tertiary structures [9–11], enabling them to interact with diverse DNA, RNA, or protein partners to modulate processes at the levels of chromatin, transcription, translation and/or signalling transduction (Fig. 1A). miRNAs is the largest subset of sncRNAs known to be involved in CRC. miRNAs are ~22-nucleotides in

length and are processed from the introns or exons of coding or non-coding transcripts [12]. By recruiting the RNA-induced silencing complex (RISC) to specific RNA targets through sequence complementarity, miRNAs control RNA degradation and/or protein translation [13]. miRNAs are counter-regulated by lncRNAs through three mechanisms (Fig. 1B). At the miRNA biogenesis step, lncRNAs can fine-tune miRNA processing and maturation [14]. lncRNAs can also act as ‘miRNA sponges’ [15]: by base complementarity, lncRNAs can bind to specific miRNAs and sequester them away from their canonical targets. Lastly, base pairing between lncRNA and mRNAs can physically limit miRNA access to their targets [16].

In addition to controlling miRNA biogenesis and function, lncRNAs that are abundantly found in the nucleus can interact with chromatin DNA and regulate gene transcription (Fig. 1C). For instance, active transcription at ncRNA locus residing on regulatory elements such as enhancers and/or repressors can promote changes in the local chromatin architecture, resulting in activation or repression of nearby genes and/or the proper splicing of their transcripts [17]. Nuclear lncRNAs can also act *in trans*. By either base pairing with chromatin DNA to form RNA-DNA duplexes and/or tethering with DNA-binding transcription factors, lncRNAs can regulate chromatin accessibility and transcription of distal genes [18]. In the next section, we will discuss how many of these mechanisms underly ncRNA contribution to health and tumorigenesis in the intestine.

ncRNAs in epithelial proliferation checkpoints

Healthy intestinal epithelial cells (IECs) have a short life span of 3–5 days [19]. Mature IECs are replenished by newly differentiated cells derived from the transient amplifying cells residing at the base of intestinal crypts [19]. A main driver for epithelial turnover is Wnt signalling [20]. Wnt ligands binding to cell

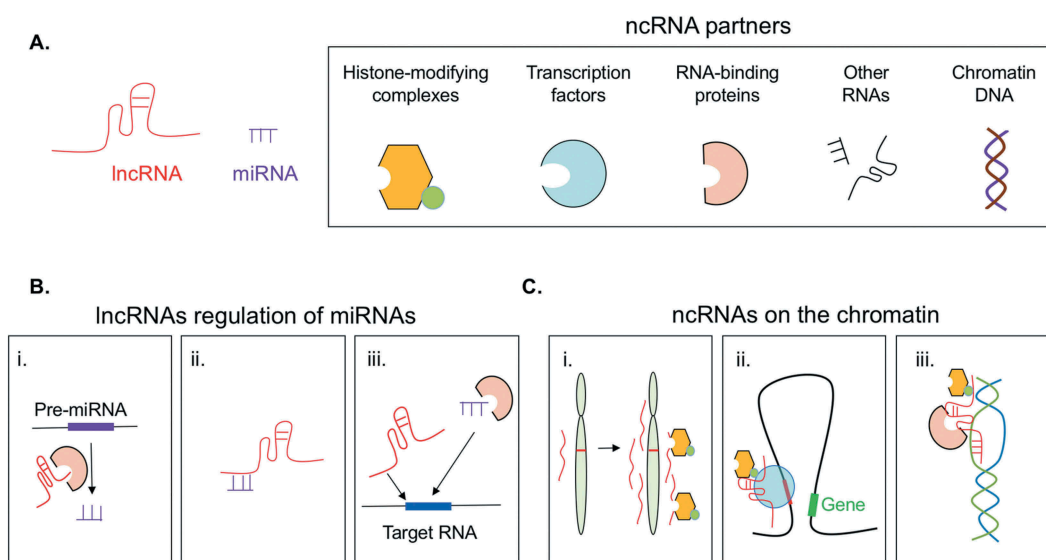


Figure 1. General principles and mechanisms underlying ncRNA functions. A. ncRNAs interact with diverse partners. B. lncRNAs counter regulate miRNAs by: i) modulating pre-miRNA processing, ii) direct sequestration, iii) competition for same target RNAs. C. lncRNAs regulate gene expression by i) modulating chromatin architecture of nearby genes *in cis*; ii) complexing with transcription factors or iii) forming RNA-DNA duplexes to regulate transcription of distal genomic loci.

surface receptors promote the translocation of β -catenin into the nucleus and the transcriptional activation of the cell proliferation program [21]. Normally, the Wnt and β -catenin pathway is tightly regulated to prevent aberrant epithelial growth by the adenomatous polyposis coli (APC) protein complex. The APC complex targets β -catenin for proteasome-mediated destruction, putting a brake on epithelial growth [22]. In addition to the APC complex, tumour suppressor p53 also holds epithelial proliferation in check [23]. p53 activates the transcription of *CDKN1A* and *PTEN* to promote cell cycle arrest and facilitate apoptosis [24]. Loss of the APC and p53 checkpoints coupled with aberrant growth factor stimulation trigger tumorigenesis in humans and mice [25–28].

p53 is known to upregulate ncRNAs with potent anti-tumour activities, including miR-145, lincRNA-p21, and the growth arrest-specific transcript 5 (*GAS5*). miR-145 helps to dampen the expression of *MYC*, which encodes a one of the driver of epithelial proliferation [29]. lincRNA-p21 helps to shut down global gene transcription by recruiting the heterogeneous nuclear ribonucleoprotein K (hnRNP-K)-containing repressive complex onto chromatin DNA, halting CRC cell cycle progression [30]. When overexpressed, lincRNA-p21 attenuates the self-renewal capacity of CRC cancer stem cells by blocking Wnt/ β -catenin signalling [31]. The p53-dependent lincRNA *GAS5*, encodes a cluster of small nucleolar RNAs (snoRNAs), is implicated in cell cycle arrest [32–34]. In response to growth factor stimulation, the insulin receptor substrate-1 (*IRS-1*) and AKT signalling triggers p53 ubiquitination and degradation, promoting epithelial proliferation. Under homeostasis, miR-203a-3p and miR-126 negatively regulate *IRS-1* and β -catenin transcripts to limit AKT-induced degradation of p53 and prevent aberrant proliferation [35,36].

ncRNAs in CRC growth and EMT

Tumour cells upregulate a unique set of lncRNAs with oncogenic activities to bypass the APC and p53 checkpoints, thereby driving

cancer cell proliferation and EMT. At the transcription level, two well-studied examples include the nuclear lncRNAs *DUXAP10* and *CCAT1-L*. lncRNA *DUXAP10* is a transcriptional silencer. By forming a complex with the histone demethylase lysine-specific demethylase 1 (LSD1) complex, *DUXAP10* shuts down the expression of p53 target genes, including *CDKN1A* and *PTEN* [37]. *CCAT1-L* is a 5200 nt lncRNA that is also highly upregulated in CRC [38]. It is transcribed 515 kb upstream of the *MYC* locus. *CCAT1-L* acts as a transcriptional regulator of *MYC* by binding to CTCF proteins and enhancing the interaction between the *MYC* promoter and its distal enhancers [38].

At the post-transcriptional level, CRCs hijack a diverse set of ncRNAs to evade cell cycle checkpoints. Several snoRNAs, ranging from 60 to 170 nucleotides in size, have been implicated in CRC (summarized in Table 1) [32,33,39–43]. Ectopic expression of *SNORA42* strengthens CRC proliferation, invasion, and migration, while the inhibition of *SNORA42* by CRISPR-Cas9 suppresses cell proliferation and invasion capacities [34]. The small nucleolar RNA host genes (*SNHG*s) encoding multiple snoRNAs are also involved in CRC. For

Table 1. ncRNAs involved in epithelial growth and transformation.

Target Pathway	lncRNAs	miRNAs	snoRNAs
PI3K/AKT/MYC	CCAT [38]	miR-203a-3p [60]	SNORD126 [32]
	GHET1 [59]	miR-126 [61]	SNHG15 [42]
WNT/ β -Catenin	lincRNA-21 [31]	miR-145 [29]	SNHG1 [39,40]
	CCAL [62]	miR-101 [66]	
	CTD903 [63]	miR-34 [67]	
	CASC11 [64]	miR-224 [68]	
	TINCR [65]	miR-146a [69]	
		miR-490-3p [70]	
p53/p21/PTEN	DUXAP10 [37]	miR-17-5p [71]	GAS5/SNORD44 [33]
	ZFAS1 [72]	miR-21 [75]	
	MEG3 [73]		
	BANCR [74]		
	lincRNA-p21 [30]		
EMT	AB073614 [76]	miR-200s [78]	SNHG6 [43]
	TUG1 [77]		

instance, SNHG1 is a lncRNA encoding 8 snoRNAs, and is significantly upregulated in CRC [43]. SNHG1 sequesters miR-145/miR-154-5p [44,45] to promote *MYC* expression and cell cycle progression [40,41]. CRCs also overexpress miR-21 to target *CDKN1A* and *PTEN* transcripts for degradation [46].

EMT in CRCs is initiated by ZEB proteins [47,48]. *ZEB1* transcripts are targeted for degradation by members of the miR-200 and miR-26a families in healthy epithelium [49,50]. miR-200 and miR-26a can be counteracted by lncRNAs, H19 and lncRNA-ATB acts as sponges for miR-200 to prevent *ZEB1* transcript degradation and promote EMT and cancer progression [51–57]. And lncRNA SNHG6 counteracts miR-26a through similar mechanism to drive CRC invasion, migration and EMT [58]. Future studies will be needed to elucidate the exact molecular mechanisms underlying their contributions to CRC.

ncRNAs and inflammation

CRC is tightly associated with inflammation [79]. Patients with inflammatory bowel diseases (IBD) are at a higher risk of developing CRC [80]. Elevated immune-modulatory cytokines not only influence the function of immune populations infiltrated to the lesion, but also act directly on cancer cells to promote disease progression. Known CRC-related cytokines and their regulation by sncRNAs and lncRNAs are summarized in Table 2. The contributions of miRNAs to inflammatory cytokine expression have been extensively reviewed elsewhere and beyond the scope of this review [81]. In the next section, we will summarize lncRNA regulation of pro-inflammatory cytokines involved in CRC [82], including interleukin-6 (IL-6), tumour necrosis factor (TNF α), and interferon-gamma (IFN γ) (Fig. 2).

Increased expression of IL-6 is linked to advanced stages of CRC and decreased patient survival [98,99]. IL-6 activates the STAT3 signalling cascade [100] and turns on gene programs involved in CRC proliferation, migration, and angiogenesis [101–103]. In addition, IL-6 promotes the recruitment and expansion of immunosuppressive myeloid-derived suppressor cells (MDSCs) and inhibits the maturation of human dendritic cells in the tumour environment [104,105]. Neutralization

of the IL-6 receptor as well as the genetic ablation of IL-6 and/or STAT3 reduces tumorigenesis in mouse models of CRC [102,106]. IL-6 expression is regulated by multiple lncRNAs. lncRNA-Cox2 and lncRNA NEAT1 promotes IL-6 expression via distinct mechanisms. lncRNA-Cox2 is induced by Toll-like receptor ligands and partners with the heterogeneous nuclear ribonucleoproteins hnRNP-A/B and hnRNP-A2/B1 to drive *Il6* transcription in the nucleus [107,108]. lncRNA NEAT1, on the other hand, acts further upstream and potentiate IL-6 expression by promoting the activation of the JNK1/2 and ERK1/2 signalling cascades [109].

Other lncRNAs can limit IL-6 expression through negative feedback loops to prevent exacerbated inflammation. For example, the Toll-like receptor-induced lncRNA Mirt2 associates with TRAF6 in the cytoplasm and blocks its ubiquitination. Loss of TRAF6 ubiquitination diminishes the activation of NF κ B and MAPK, putting a brake on *Il6* transcription [110]. In the nucleus, three additional lncRNAs help to keep *Il6* transcription in check. lncRNA Lethe acts as a decoy partner for NF κ B and blocks its recruitment on the *Il6* promoter [111]. lnc-IL7R promotes the deposition of trimethylation on lysine 27 of histone H3 and sets up a repressive chromatin environment at the *Il6* locus [112]. Lastly, lncRNA-EPS represses *Il6* expression by partnering with hnRNPL to reduce chromatin accessibility [113].

Another CRC promoting inflammatory cytokine is TNF α [114]. TNF α signalling leading to the activation of NF κ B drives CRC survival, proliferation, invasion, and metastasis [115]. Genetic ablation of the TNF receptor protects mice against chemical-induced colon tumour [114] and limits liver metastasis of transplanted CRC in mouse models [116]. Human IBD and CRC patients treated with anti-TNF α had less intestinal inflammation and decreased tumour burden [117,118]. TNF α expression is regulated by three lncRNAs. The TNF α and hnRNPL-related immunoregulatory lincRNA, *THRIL*, works together with hnRNPL to promote *TNF* transcription [119]. lnc-13 and lncRNA-CD244 negatively regulate *Tnf* expression in mice and humans, respectively, through distinct mechanisms. *lnc-13* associates with hnRNPD to recruit the histone deacetylase, HDAC1, to remove the activation marks on the *Tnf* promoter [120]. In contrast, lncRNA-CD244 turns off *TNF* transcription by partnering with the enhancer of zeste homolog 2 (EZH2)-containing complex to deposit repressive tri-methylation marks on lysine 27 of histone H3 on the *TNF* locus.

Similar to IL-6 and TNF α , IFN γ also promotes CRC pathogenesis [121]. IFN γ signalling induces expression of immune checkpoint molecules, including PD-L1 [122], which promotes evasion from anti-tumour immune responses [123]. Transcription of the *Ifng* gene is regulated by lncRNA NeST, also known as *Ifngas1* or *Tmevpg1* [124]. The *NeST* locus is associated with an IBD susceptibility related SNP, rs7134599. Accordingly, elevation of NeST expression in ulcerative colitis patients positively correlates with enhanced IFN γ levels [125]. However, the link between rs7134599 and NeST to CRC has not been clearly demonstrated [126]. Mechanistically, NeST works together with the methyltransferase WDR5 to promote trimethylation on lysine 4 of histone H3 and transcriptional activation of the *Ifng* gene [124]. Together, lncRNAs and their

Table 2. ncRNAs involved in inflammatory cytokine expression.

Inflammatory cytokines	lncRNAs	miRNAs
IL-6	Lethe [111]	miR-21 [84]
	lincRNA-Cox2 [108]	miR-24 [85]
	lincRNA-EPS [113]	miR-26a [86]
	lnc-IL7R [112]	miR-124 [87]
	MARCKS [83]	miR-147 [88]
	Mirt2 [110]	
	NEAT1 [109]	
	ROCK1 [83]	
	lnc13 [120]	miR-24 [85]
	THRIL [119]	miR-124 [87]
TNF		miR-147 [88]
		miR-29 [86]
IFN γ	lncRNA-CD244 [89]	miR-155 [90]
	NeST [124]	miR10a [92]
IL-8	NEAT1 [109]	miR200 [93]
	PANDA [91]	miR203 [94]
		miR302 [95]
IL-1 β	LSINCT5 [96]	miR-233 [97]
	Mirt2 [110]	

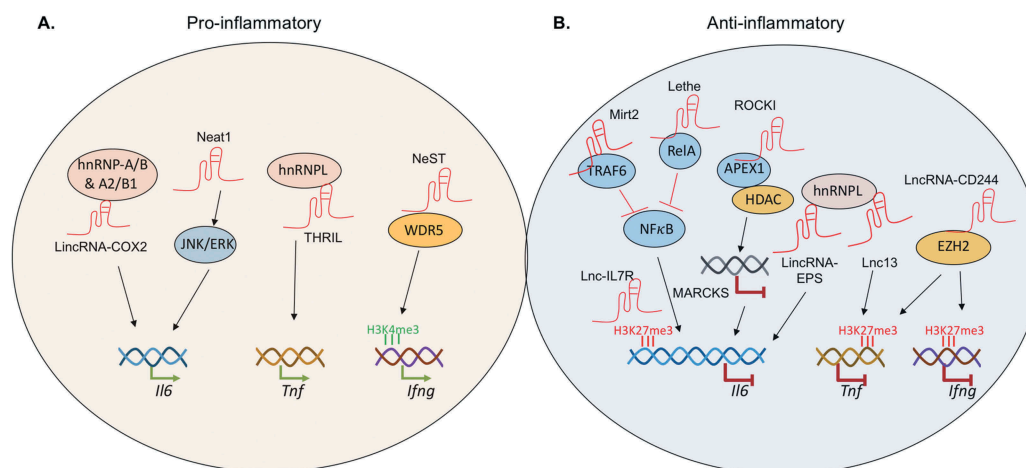


Figure 2. LncRNAs as positive and negative regulators of inflammation. A. Different lncRNAs recruit distinct partner proteins to regulate inflammatory cytokine expression. *Il6* transcription is augmented by lincRNA-Cox2 and lincRNA NEAT1. *Tnf* expression is upregulated by lincRNA THRIL. Transcription of the *Ifng* locus is regulated by lincRNA NeST. B. In humans, *Il6* transcription is negatively regulated by Lnc-17R and ROCK1. In mice, *Il6* transcription is negatively regulated by lincRNA Mir2 and Lethe. Lnc13 interacts with hnRNPL to block the transcription of *Tnf*. LncRNA-CD244 recruits EZH2 to deposit repressive histone marks and shut down transcription at both the *TNF* and *IFNG* loci.

associated transcription factors and epigenetic modifiers are critical regulators of inflammatory cytokine expression. Future studies will be needed to fully assess each of their contribution to CRC *in vivo*.

Emerging tools for studying ncRNAs

ncRNAs accomplishes a diverse range of biological functions by interacting with other RNAs, proteins, and chromatin DNA (Fig. 1). However, we have limited understanding of how these interactions contribute to ncRNA biology in the context of health and diseases. Emerging tools are now allowing researchers to tackle these challenges in the field. For instance, RNA–RNA interactions can be mapped using the MS2-tagged RNA affinity purification (MS2-TRAP) system *in vitro* as well as the cross-linking [127], ligation, and sequencing of hybrids (CLASH) assay *in vivo* [128]. Protein partners of ncRNAs can be elucidated using the comprehensive identification of RNA-binding proteins by mass spectrometry (ChIRP-MS) [129], click chemistry-assisted RNA-interactome capture (CARIC) [130], and the crosslinking and immunoprecipitation (iCLIP/eCLIP) assays [131,132]. ncRNA–DNA interactions on the chromatin can be revealed using the chromatin-associated RNA sequencing (ChAR-seq) [133] and the *in situ* global RNA interactions with DNA captured by deep sequencing (GRID-seq) approaches [134]. Furthermore, ncRNA secondary and tertiary structures are important determinants for the specificity and affinity of ncRNAs for their interaction partners. Future studies will need to better elucidate ncRNA structural information inside living cells with approaches such as the selective 2'-hydroxyl acylation analysed by primer extension and sequencing (SHAPEseq) [135]. Together with cryogenic electron microscopy, researchers will soon be able to gain new lights on additional general principles underlying ncRNA biology.

Discussion

The human and mouse genome is estimated to have over 2,000 miRNAs [136], 50,000 lncRNAs [137], and 1,000 RNA-binding proteins [138]. However, only a handful has been characterized in the context of CRC. For instance, we know relatively little about the involvement of ncRNAs in the production of anti-inflammatory cytokines, such as IL-10 and TGF β , which are known for negative regulating intestine inflammation [139,140]. In addition, there are several other families of ncRNAs with newly defined roles in CRC, such as the tRNA and tRNA-derivatives (reviewed in [141]). But the mechanistic details of their contribution remained to be elucidated. To close these knowledge gaps, high-throughput gain and loss of function screens, including the use of the latest CRISPR-Cas9 technologies [142], will be critical in future studies. Molecular insights can be revealed using a combined molecular, biochemical, genetic and genomic approach. Future studies should also evaluate whether the ncRNA mechanisms of action thus far are conserved or unique in different cell types under steady state and across different disease conditions. And, better understanding of how ncRNAs contribute to the crosstalk between tumour cells and their local environmental cues will facilitate the development of novel targets against inflammation-driven tumorigenesis.

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Disclosure of potential conflicts of interest

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