



Review

Role of non-coding RNAs as novel biomarkers for detection of colorectal cancer progression through interaction with the cell signaling pathways



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ABSTRACT

Colorectal cancer (CRC) is one of the most common types of cancer which affects the colon and the rectum. Approximately one third of annual CRC mortality occurs due to the late detection of this type of cancer. Therefore, there is an urgent need for more powerful diagnostic and prognostic tools for identification and treatment of colorectal tumorigenesis. Non-coding RNAs (ncRNAs) have been implicated in the pathology of CRC and also linked to metastasis, proliferation, differentiation, migration, angiogenesis and apoptosis in numerous cancers. Recently, attention has turned towards ncRNAs as specific targets for diagnosis, prognosis and treatment of various types of cancers, including CRC. In this review, we have tried to outline the roles of ncRNAs, and their involvement in signaling pathways responsible for the progression of CRC.

Abbreviations: 3'-UTR, 3'-untranslated region; AKAP-9, PRKA kinase anchor protein 9; APC, adenomatous polyposis coli; CCAT, colon cancer-associated transcript; CCAT1-L, CCAT1-the long isoform; ceRNAs, competing endogenous RNAs; CIN, chromosomal instability; circRNAs, circular RNAs; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; EMT, epidermal to mesenchymal transition; H3K4me2, histone H3 dimethyl Lys4; H3K27me3, histone H3 tri-methylated at lysine 27; HCC, human hepatocellular carcinoma; HMGAl, high-mobility group A1; HOTAIR, HOX transcript antisense RNA; HULC, high up-regulation in liver cancer; lncRNAs, long non-coding RNAs; LSD1, lysine-specific demethylase; MALAT1, metastasis associated with lung adenocarcinoma transcript 1; MEG3, maternally expressed gene 3; miRISC, miRNA-RISC complex; miRNAs, microRNAs; ncRNA, non-coding RNA; PCAT-1, prostate cancer-associated ncRNA transcripts 1; piRNAs, Piwi-interacting; RNase P, ribonuclease P; Piwi, P-element-induced wimpy testis; PRC2, polycomb repressive complex 2; Prdxs, peroxiredoxins; PTGS, Post-transcriptional gene silencing; RB, Retinoblastoma; RISC, RNA-induced silencing complex; RITS, RNA-induced transcriptional silencing; rRNAs, ribosomal RNAs; shRNA, short hairpin RNA; siRISC, siRNA-RISC complex; siRNAs, short/small interfering RNAs; snRNAs, short noncoding RNAs; snRNAs, small nuclear RNAs; snoRNAs, small nucleolar RNAs; STIM1, stromal interaction molecule 1; TEs, transferable elements; TGF- β , transforming growth factor- β ; TNM, tumor node metastatic; tRNAs, transfer

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1. Background

Colorectal cancer (CRC) accounts for the third most common cancer by incidence and also the second leading cause of mortality in the world. Despite the progress made in diagnosis and treatment over last decade, the five-year survival rate is still around 65% (Siegel et al., 2014). Approximately, 50% of the mortality rate of CRC has been linked to metastasis (Lothe et al., 1993; Corté et al., 2012). The incidence of CRC has increased significantly in developing countries, as well as in the Southern and Eastern Europe during last decade. To develop CRC, a number of heterogeneous cell types, with different specifications, are involved. These cells may transform to cancer cells, in the large intestine, rectum, and appendix. Various environmental and genetic factors have been also linked to the etiology of CRC (Rickert et al., 1979; Gutman and Fidler, 1995; Esmailzadeh et al., 2017).

Despite all efforts and remarkable advances for improving CRC treatment via surgery and chemotherapy, CRC prognosis is not well done. Also, cancer relapse or metastatic recurrence frequently occurs after surgery. Unfortunately delay in diagnosis is one of the most critical issues in CRC. Accumulating evidences show that noncoding RNAs (ncRNAs) exert essential roles in the development and progression of CRC.

Non coding RNAs (ncRNAs) are the special sorts of RNA molecules which are not translated. Certain types of ncRNAs are ubiquitously found in all cell types which be considered as housekeeping RNAs, e.g. ribosomal, transfer, small nuclear, small nucleolar RNAs, and ribonuclease P RNAs. Regulatory ncRNAs or functional RNAs are another type of ncRNAs responding to the external cues, involved in epigenetic process of regulating gene expression. ncRNAs are divided into three main groups including, the short/small non-coding RNAs, the long non-coding RNAs (lncRNAs), and the circular RNAs (circRNAs) (Eddy, 2001) (Fig. 1).

Numerous ncRNAs display tumor-specific expression, hence they can be considered as useful biomarkers for diagnosis and excellent candidates for therapeutic applications in CRC and other kinds of cancers (Arun et al., 2018; Følseteder et al., 2018).

2. The short non-coding RNAs

The short non-coding RNAs (sncRNAs) are divided in three main sub-classes, including: microRNAs (miRNAs), short interfering RNAs (siRNAs), and piwi-interacting RNAs (piRNAs). sncRNAs play a role in gene expression regulation including: gene silencing through RNA interference (RNAi), and epigenetic modifications (including chromatin remodeling by encouraging heterochromatin formation through histone modification or targeting DNA, such as methylation of cytosine at the respective promoters) (Ragusa et al., 2015).

3. Deregulation of miRNAs in CRC

miRNAs are 18–25 nucleotide-long RNAs play important roles in regulation of multiple metabolic and cellular pathways through interacting with their target genes especially to control cell proliferation, differentiation, apoptosis and survival. Several miRNAs are termed as oncomiRs, since they are linked to oncogenesis events, in CRC. OncomiRs may either act as oncogenes or tumor suppressors. Their up-regulation or down-regulation, aberrant function or loss of function may be involved in development or progression of certain malignancies (Fendler, 2011; Rukov and Shomron, 2011). In addition, certain miRNAs may have oncogenic influences by down-regulating certain tumor-suppressors or genes involved in DNA repair or apoptosis. Moreover, certain miRNAs may display anti-cancer effects by switching off the mRNA of specific proto-oncogene targets (Montano, 2011). Background studies reveal numerous miRNAs are related to the etiology and progression of CRC. miRNAs regulate certain components of various oncogenic pathways that are linked to the incidence or progression

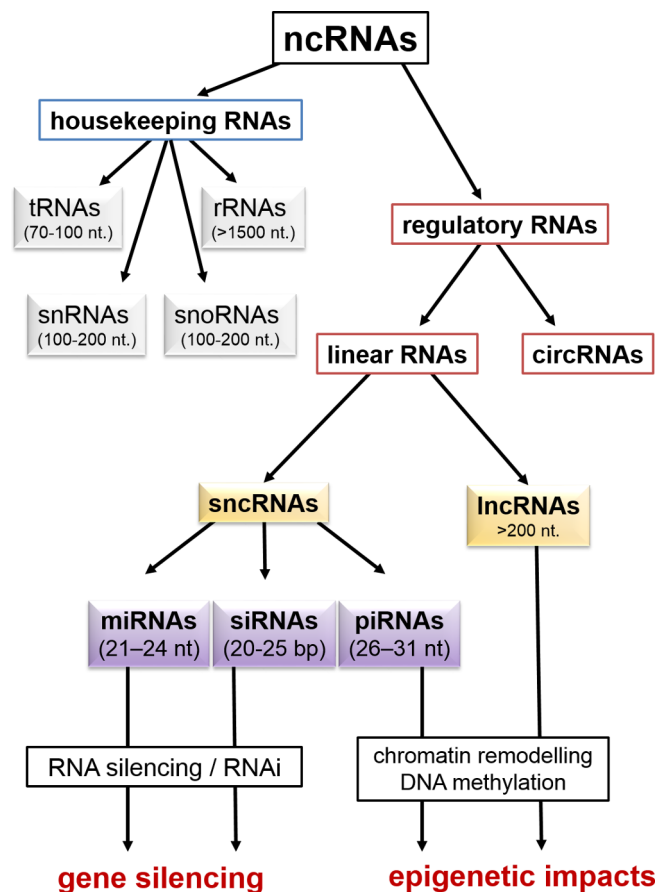


Fig. 1. Schematic classification of ncRNAs and their regulatory features. ncRNAs may incorporate in gene expression regulation, at the pre-transcriptional (epigenetic regulation), transcriptional, post-transcriptional, translational and even post translational levels. The epigenetic impacts of ncRNAs may include targeting DNA (e.g. via promoting DNA methylation), or chromatin remodelling (provoking histone modifications such as stimulation of histone deacetylases). More particular gene regulations may take place through, targeting special transcriptional factors (inducers/inhibitors), targeting complementary mRNA molecules (referred as RNA silencing or RNA interference), or even targeting special components of a signaling pathway. Although the circular RNAs (circRNAs) are classified as ncRNAs, the vast majority of them arise from protein-coding DNAs. The exact biological function of circRNAs is not clear, but it is known that they are derivatives of deficient splicing. Note that the lncRNAs may also fall into further categories, based on their structures or functions, including double-stranded RNAs (dsRNA, such as siRNAs), single-stranded (ssRNA, such as miRNA and piRNA), intronic (intragenic), exonic, intergenic, bidirectional, sense and antisense.

of CRC, including WNT, EGFR and the transforming growth factor beta (TGF- β) signaling pathways as well as the TP53 complex (Mohammadi et al., 2016) (Table 1, Supplementary information).

In vast majority of CRCs, mutations activate the Wnt/ β -catenin pathway. The germ line loss-of-function mutations of APC, as a tumor suppressor, are linked to the majority of familial adenomatous polyposis (FAP) syndrome (Fig. 2). Approximately 60% to 80% of the sporadic colorectal adenomas and adenocarcinomas harbor APC mutations (Corté et al., 2012; Peng et al., 2017). Nagel and colleagues demonstrated that miR-135a/b down-regulates the expression of APC via targeting the 3'-untranslated region (3'-UTR), thereby stimulating Wnt pathway activity. This finding reveals the negative association between mRNA levels of APC and expression of miR-135a&b in colorectal adenomas and carcinomas (Nagel et al., 2008a; Clevers et al., 2014a; Siegel et al., 2017). Other studies also demonstrated clinical significance of miRNAs, such as let-7g, miR-15a, miR-215, miR-129, miR-181b, miR-

Table 1
The list of important miRNAs involved in modulation of CRC.

| miRNA | Target | Signaling pathway | Expression | Ref |
|------------|-----------------------------------|--------------------|------------|--|
| Let-7a | KRAS | EGFR | Decreased | (Sebio et al., 2013) |
| miR-106a | TGFBR2 | TGF- β | Increased | (Moustakas and Heldin, 2009) |
| miR-125 | P53 | TP53 | Increased | (Nishida et al., 2011) |
| miR-126 | PI3K | EGFR | Decreased | (Danielsen et al., 2015) |
| miR-135a/b | APC | Wnt | Increased | (Clevers et al., 2014) |
| miR-34 | SIRT1-p53, CTNBN1, c-Myc, Cyclin1 | Multiple pathways | Decreased | (Nagel et al., 2008a; Yamakuchi et al., 2008; Biegging et al., 2014) |
| miR-145 | KRAS, c-Myc, cyclin1 | Wnt, EGFR | Decreased | (Pagliuca et al., 2013) |
| miR-26b | c-Myc, Cyclin1 | Wnt | Decreased | (Nagel et al., 2008a) |
| miR-146a | NUMB | Wnt | Increased | (Hwang et al., 2014a) |
| miR-143 | KRAS | EGFR | Decreased | (Pagliuca et al., 2013) |
| miR-181a | KRAS | EGFR | Increased | (Ota et al., 2012a) |
| miR-210 | KRAS | EGFR | Increased | (Ota et al., 2012a) |
| miR-21 | PTEN | EGFR, TGF- β | Increased | (Sheng et al., 2016a) |
| miR-32 | PTEN | EGFR | Increased | (Wu et al., 2013) |
| miR-92 | PTEN | EGFR | Increased | (Zhang et al., 2014) |
| miR-148b | P53 | TP53 | Increased | (Wang et al., 2015a) |
| miR-17 | TGFBR2 | TGF- β | Increased | (Moustakas and Heldin, 2009; Zhang et al., 2014) |
| miR-20a | TGF- β | UP | Increased | (Moustakas and Heldin, 2009) |
| miR-301a | SMAD4 | TGF- β | Increased | (Moustakas and Heldin, 2009; Bellam and Pasche 2010) |
| miR-130a | SMAD4 | TGF- β | Increased | (Bellam and Pasche 2010) |
| miR-454 | SMAD4 | TGF- β | Increased | (Bellam and Pasche 2010) |
| miR-25 | SMAD7 | TGF- β | Increased | (Li et al., 2013) |

140, and miR-200c, in CRCs (Yang et al., 2017a).

Ectopic expression of miR-145 causes an increase in cytoplasmic level of β -catenin (Fig. 2). On the other hand, miR-34a/b/c and miR-26b inhibit the expression of *LEF1*, targeting its 3'-UTR (Nagel et al., 2008a; Yamada et al., 2013). A number of miRNAs, including the miR-34 family, which transcriptionally up-regulate TP53, inhibit the TCF/LEF family complex that are nuclear targets of β -catenin (also like *LEF1*) (Schepeler et al., 2012). During epithelial-mesenchymal transition (EMT), Snail1/2 expression is up-regulated. This effect shifts the asymmetric cell division to symmetric situation, thereby reduces the rate of cellular differentiation while cell proliferation is busted. Snails also provoke miR-146a expression via mechanical interaction with the complex between β -catenin and transcription factor 4 (TCF-4). Consequently, the over-expressed miR-146a stabilizes β -catenin by repressing *Numb*, which establish a feedback circuit towards maintaining β -catenin and switching asymmetric to symmetric cell division in CRC stem cells (Hwang et al., 2014a; Peng et al., 2017) (Fig. 2, For more information on this pathway, please see the supplementary information).

Recently, the role of miRNAs in KRAS-induced CRC has been highlighted (Fig. 2). Let-7, miR-143, and miR-145 act as tumor suppressors that inhibit KRAS expression, whereas oncogenic miRNAs such as miR-181a and miR-210 are upregulated by KRAS (Ota et al., 2012a; Pagliuca et al., 2013; Sebio et al., 2013). It has been shown that over-expression of let-7, in DLD-1 human colon cancer cells, affects their growth by decreasing the level of RAS and c-Myc proteins (Akao et al., 2006). The PI3K/AKT signaling pathway plays a role in the development and progression of CRC tumors (Danielsen et al., 2015). Several miRNAs have been reported to target the PIK3/AKT in the downstream of the EGFR signaling pathway (Tsang and Kwok, 2009). The expression of miR-126 is frequently decreased in CRC. miR-126 promotes PI3K activity that is commonly limited due to the higher level of PIK3 regulatory subunit- β (PIK3R2) in the normal colon epithelium (Danielsen et al., 2015). PTEN (Phosphatase and tensin homolog), is another tumor suppressor that negatively regulates PIK3/AKT pathway, deactivated in many primary and metastatic malignancies by mutations and/or deletions (Guo et al., 2008). Several miRNAs such as miR-21 (Sheng et al., 2016a), miR-32 (Wu et al., 2013) and miR-92a belong to the miR-17-92 cluster, target *PTEN* transcripts in CRC (Zhang et al., 2014) (Fig. 2, please see more explanation in supplementary information).

The miR-34 family and miR-34a, in particular are known as the p53-inducible miRNAs (Biegging et al., 2014). Their expressions have been reported to be altered in CRC. For instance, miR-34a is increased in CRC

patients. *SIRT1* is overexpressed in CRC. SIRT1, deacetylates p53, thereby prevents p53-mediated cell cycle arrest and apoptosis. It has been demonstrated that miR-34a acts as a tumor suppressor, probably via suppressing *SIRT1* expression. Therefore, once miR-34a targets *SIRT1*-induced apoptosis in the wild-type colon cancer cells, a positive feedback loop is established due to the activities of TP53 and miR-34 (Yamakuchi et al., 2008). The TP53 itself is regulated by various miRNAs. For instance, miR-125b has been found to be a negative regulator of p53 in CRC. Accordingly, overexpression of miR-125b affects the progression of CRC (Nishida et al., 2011). It is documented that p55PIK, a PI3K isoform, contributes to the tumor growth, is amplified significantly in CRC. On the other hand, miR-148b significantly suppresses *p55PIK* expression, via binding to the 3'-untranslated region of *p55PIK*.

Notably, TP53 stimulates miR-148b through binding to its promoter. As a result, the p53/miR-148b/*p55PIK* pathway is suggested as a potential therapeutic target for treating cancers involved p53 mutations (Wang et al., 2015a).

Several miRNAs have been identified as regulators of TGF β R2, such as miR-17-5p, miR-20a, miR-106a and miR-301a (Moustakas and Heldin, 2009). The oncogenic miR-17-92 cluster comprises miR-17, miR-18a, miR-19a, miR-19b, miR-20a and miR-92a, is indirectly induced by c-Myc and may be overexpressed in various types of cancers. The miR-17-92 cluster inhibits TGF- β pathway and its downstream elements (such as TGF β R2 and SMAD4) as well as TGF- β -responsive genes (Mestdagh et al., 2010; Kim et al., 2013). The expression of miR-130a, miR-301a, and miR-454 are frequently increased in the CRC tissues, which have been shown to target *SMAD4* and promote cellular proliferation and migration (Bellam and Pasche, 2010). Of note that the expression of miR-25 is reduced in CRC resulting in the activation of SMAD7, a negative regulator of the TGF- β signaling pathway, ultimately leading to increased cell division rates and metastasis (Li et al., 2013) (Fig. 2, for more description about the TGF- β signaling pathway, please see the supplementary information).

4. Predicted role of small interfering RNAs in CRC

siRNAs are double-stranded RNAs (dsRNAs) with 20–25 base pairs in length responsible for the RNA interference (RNAi) event. They emerge from the cleavage of dsRNAs precursors catalyzed by dicer, a special endo-ribonuclease belonging to RNase III family (Carthew and Sontheimer, 2009; Wang et al., 2015d).

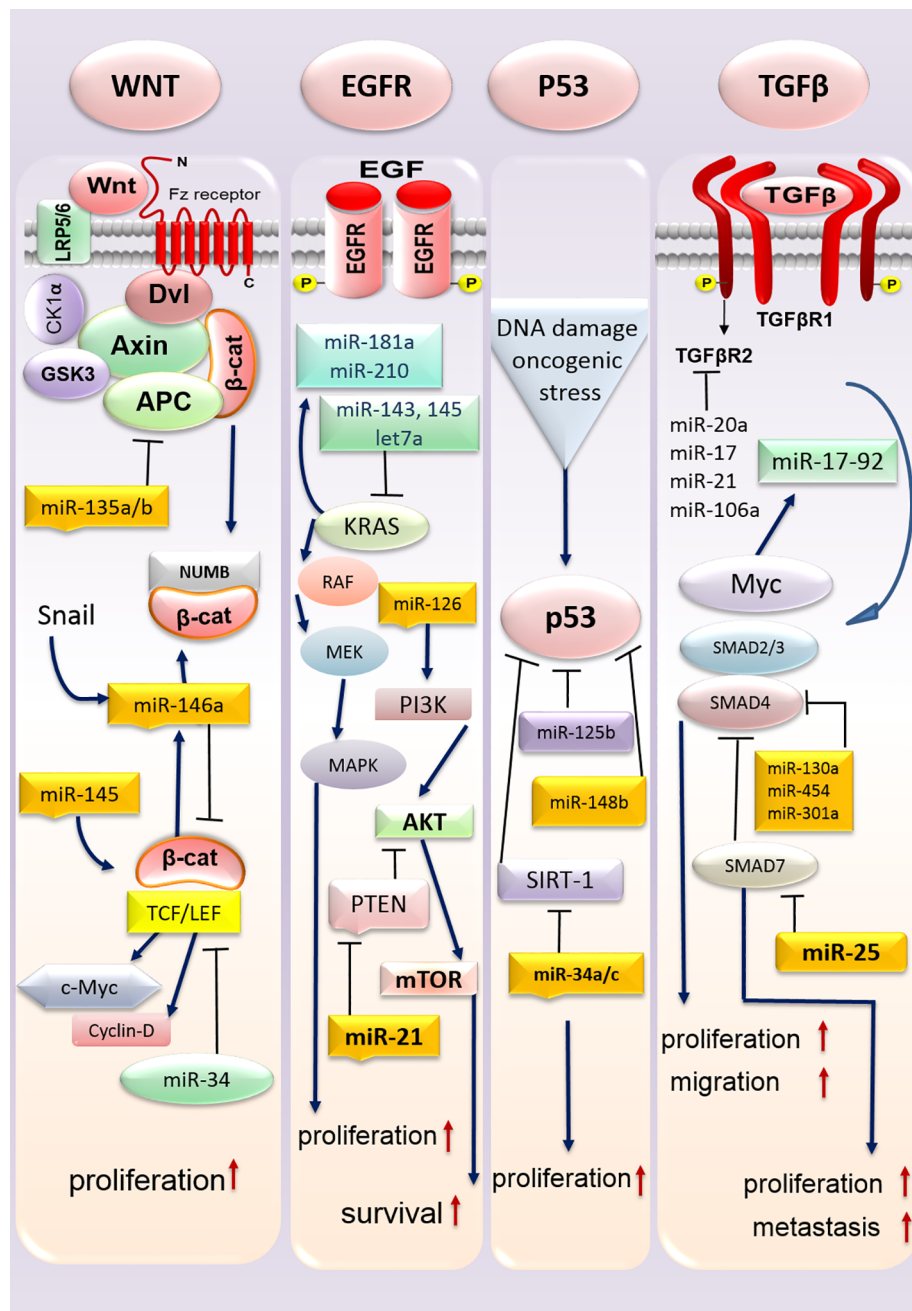


Fig. 2. Schematic representation of EGFR, TGF- β , canonical Wnt signaling pathways, the p53-mediated response to DNA damage and oncogenic stress and their modulation with a number of miRNAs. As indicated there are a number of miRNAs which targets the constituents and mediators of several important pathways thereby modulates their activities. Detailed is written in the body of manuscript.

Stromal interaction molecule 1 (STIM1), a transmembrane protein localized in the endoplasmic reticulum mediates Ca^{2+} influx after depletion of intracellular Ca^{2+} stores by gating of store-operated Ca^{2+} influx channels. Therefore, STIM1 acts as a calcium sensor during calcium signaling. Increased expression of *STIM1* is reported in aggressive CRC cells lines. Accumulating evidence indicate that overexpression or ectopic expression of *STIM1* is associated with the metastatic potential and EMT-induction and progression of CRC, both *in vitro* and *in vivo*. Accordingly, siRNA- or miRNA-mediated repression of *STIM1* (e.g. direct targeting by miR-185), diminishes metastasis of CRC cells (Zhang et al., 2015).

5. Piwi-interacting RNAs (piRNAs) play a role in CRC progress

piRNAs are a novel type of small non-coding RNA (sncRNAs) with 26–31 nucleotides. They specifically interact with the P-element-induced wimpy testis (Piwi) protein. These non-coding single strand RNAs can control and inactivate transposable element (TEs) such as retrotransposons through epigenetic and post-transcriptional gene silencing, generally to protect the genome in germline cells. Otherwise, the uncontrolled expression of TEs may lead to loss of genome integrity (Levin and Moran, 2011; Sato and Siomi, 2013). Recent studies have shown that TEs and piRNAs play crucial roles in human carcinogenicity (Assumpção et al., 2015; Moyano et al., 2015). piR-651 is over-expressed in the CRC and gastric cancer tissues (Cheng et al., 2011) and piRNAs have been shown to be the most important determining risk

factor in CRC. The occurrence of the SNP rs11776042 in piR-015551, which can be generated from a kind of lncRNA called LNC00964-3, was exceptionally associated with a reduced risk of CRC in an additive model. This result demonstrated that piR-015551 could be involved in the progress of CRC (Wang et al., 2015b).

6. Circular RNAs affect the progress of CRC

Circular RNAs (circRNAs) are covalently closed loop of RNAs that are classified as ncRNA molecules. They commonly originate from splicing errors in RNAs that code for proteins. Recently, increasing attentions have been turned to the particular features and capacities of circRNAs in pathologic states. circRNAs play important roles in the regulation of gene expression at transcriptional or post-transcriptional levels. Some circRNAs function as very stable sponges for particular miRNAs, such as CIRS-7 and SRY for miR-7 and miR-138. They are involved in challenging endogenous RNA networks (Li et al., 2015). In contrast to classical competing endogenous RNAs (ceRNAs), circRNAs have no available termini, making them stable against miRNA-mediated RNA degradation or other exonucleolytic activities. A number of studies, have shown that the ratio of the circRNA isoforms in the normal samples are higher than those of tumors. In this regard, it has been show that some circRNAs, such as circ_001569 effect on proliferation and invasion in cancer cell line. Xia et al showed this circ_001569 through miR-145 play regulatory role in proliferation and cellular invasion of CRC (Xie et al., 2016a).

7. Long non-coding RNA (lncRNAs) play critical role in CRC progression and development

lncRNAs are another type of non-coding RNA molecules having 200 or more nucleotides (Spizzo et al., 2012). lncRNAs interact with other biomolecules like proteins, DNAs and RNAs (Prensner and Chinnaiyan 2011). These molecules, in turn, regulate gene expression at diverse epigenetic, transcriptional, and post-transcriptional levels (Saus et al., 2016). On the other hand, it has been shown that lncRNAs play a remarkable role in cell growth and death, through regulating the cell cycle and apoptosis (Mourtada-Maarabouni et al., 2009). lncRNAs are located in nucleus or cytoplasm (Ravasi et al., 2006; Ponting et al., 2009; Derrien et al., 2012). lncRNAs are divided into sense, antisense, and bidirectional, intronic and intergenic groups, based on their location in respective genes (Khalil et al. 2009; Mercer et al., 2009). Notably, their coding genes are shorter and have less exon numbers than protein coding genes (Ulitsky et al., 2011; Derrien et al., 2012; Pauli et al., 2012). lncRNAs are involved in regulation of gene expression at different levels, including transcriptional and post-transcriptional levels. The role of lncRNAs at the transcriptional level is the epigenetic inactivation of the target genes (Wutz 2011). Otherwise, the molecular mechanism of lncRNAs action at the post-transcriptional level comprises pre-mRNA processing, accelerating the degradation of mRNA, protecting mRNA from its destruction, repressing the translation of mRNA, activating the translation of mRNA, and cooperating with the miRNAs (Yoon et al., 2013). Through the appointed mechanisms, lncRNAs exert vital roles in different aspects of cellular homeostasis, such as proliferation, migration, survival, and genomic stability (Huarte, 2015). Therefore, lncRNAs may play serious roles in cancer. Enormous studies have reported the roles of lncRNAs as oncogenic factors and tumor suppressors in cancers especially CRC (Prensner and Chinnaiyan, 2011; Gibb et al., 2011). CRC-related lncRNAs have been indicated to regulate genes via several mechanisms including epigenetic modifications and the interaction between lncRNAs and miRNAs, the interaction between lncRNAs and proteins, and their function as miRNA precursors or pseudogenes (Xie et al., 2016b) (Table 2).

As mentioned earlier, the most important aspect of lncRNA function is epigenetic regulation of the target genes (Rinn et al., 2007; Yap et al., 2010; Gibb et al., 2011), in which lncRNA interacts with chromatin to

Table 2
The list of relevant lncRNAs involved in modulation of CRC.

| lncRNA | Locus | Expression | Biological function | Ref |
|---------------|----------|------------|--|--|
| HOTAIR | 12q13.13 | Increased | Promotes metastasis of CRC and function as an oncogene. | (Gupta et al., 2010; Xie et al., 2016b) |
| MEG3 | 14q32.2 | Decreased | Increases p53 levels via suppressing MDM2 levels. | (Zhang et al., 2003; Zhou et al., 2007; Xie et al., 2016b) |
| H19 | 11p15.5 | Increased | A double function of oncogene and tumor suppressor. | (Zhang et al., 2012; Matouk et al., 2013) |
| CCAT2 | 8q24.21 | Increased | Mediates c-Myc and WNT signaling, promotes metastasis, tumor growth and chromosomal instability. | (Li et al., 2009; Ling et al., 2013) |
| PCAT-1 | 8q24.21 | Increased | Promotes cell proliferation by binding to PRC2 and function as oncogene. | (Prensner et al., 2011; Ge et al., 2013) |
| PTENP1 | 9q13.3 | Decreased | A pseudogene of PTEN acts by binding to regulatory region of miRNAs function as tumor suppressor | (Poliseno et al., 2010; Wang et al., 2012) |
| HULC | 6p24.3 | Increased | By binding to miRNA regulates cell invasion and metastasis and also functions as an oncogene. | (Panzitt et al., 2007; Matouk et al., 2009) |
| Loc285194 | 3q13.31 | Decreased | Inhibits tumor growth and functions as a tumor suppressor by regulating of p53 and repressing of miR-211. | (Liu et al., 2013; Ding et al., 2015) |
| CCAT | 8q24.21 | Increased | Functions as an oncogene by impressing c-Myc transcription. | (Pomerantz et al., 2009; Kim et al., 2015) |
| CCAT1 | 8q24.21 | Increased | Promotes cell proliferation, cell invasion and migration by upregulating c-Myc and then functions as oncogene. | (He et al., 2014; Yang et al., 2017d) |
| CCAT1-L | 8q24.21 | Increased | Upregulates c-Myc, induces cell proliferation, migration and CRC tumorigenesis. | (Xiang et al., 2014) |
| MALAT1/MALAT1 | 11q13.1 | Increased | Promotes cell proliferation, migration and invasion in human colorectal malignant neoplasm. | (Ji et al., 2003) |

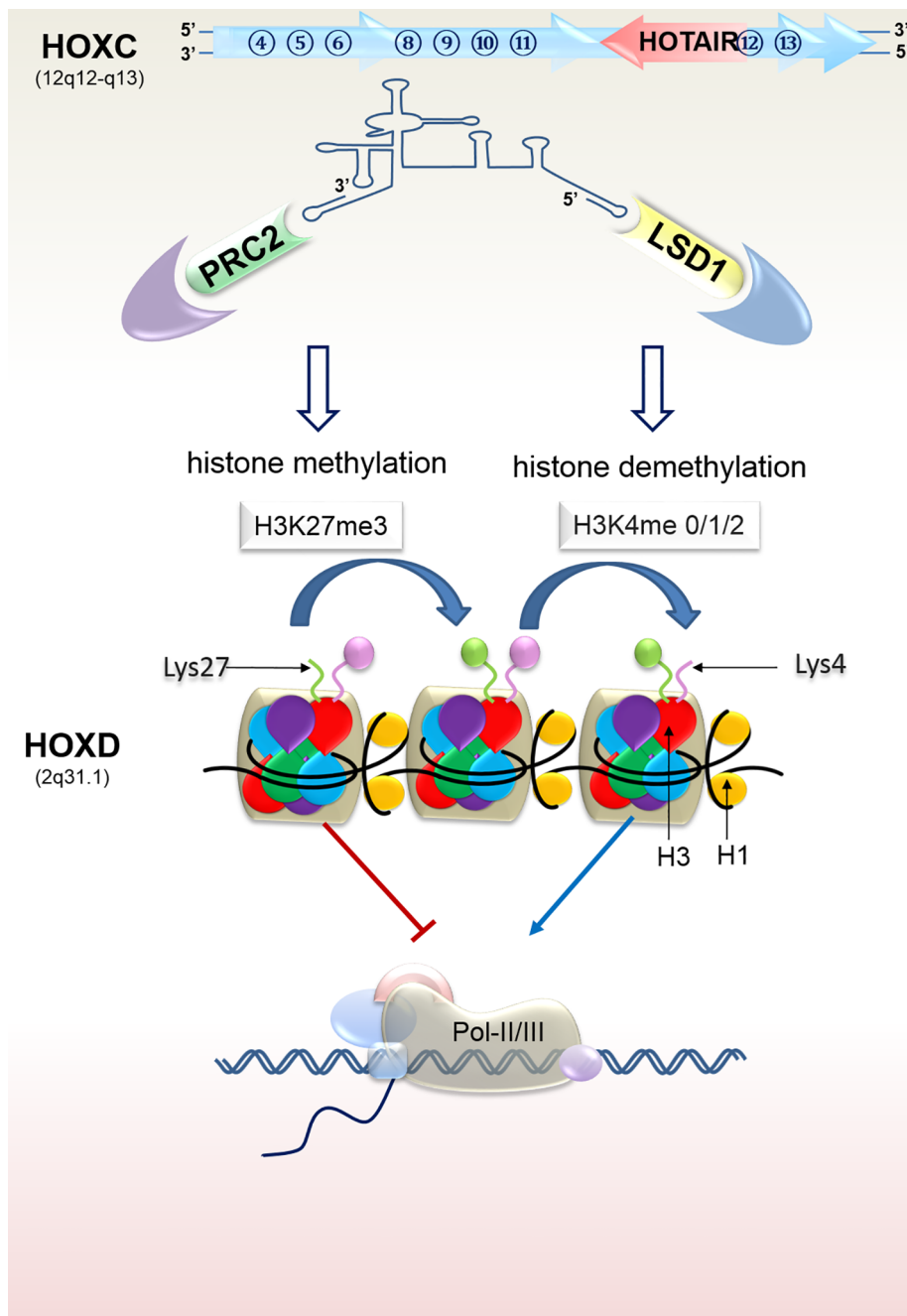


Fig. 3. HOTAIR promotes chromatin modifications related to metastasis and tumor invasiveness. HOTAIR interacts with lysine-specific demethylase 1 (LSD1), polycomb repressive complex 2 (PRC2), H3K27me3 (histone H3 tri-methylated at lysine 27) and H3K4me2 (histone H3 dimethyl Lys4); and eventually silences HOXD. Please see the text.

enroll histone-modifying enzymes e.g. DNA methylation and chromatin modification enzymes. This process eventually provides the epigenetic silencing of the target genes (Xie et al., 2016b). A number of CRC-associated lncRNAs which act through this type of regulation will be described here.

HOX transcript antisense RNA (HOTAIR) is one of the relevant regulatory lncRNAs in the human cells. Rinn et al reported that, HOTAIR is located in the HoxC cluster and has a trans-regulatory mechanism (Rinn et al., 2007). Modulation in HOTAIR plays an important oncogenic role in various cancers like breast, gastric, colorectal and cervical cancers. Therefore, its degree of expression has been considered as diagnostic and prognostic marker in several types of cancers (Hajjari et al., 2015), including CRC. These results indicate that this

lncRNA plays a key role in recurrence, metastasis of CRC (Gupta et al., 2010a; Kogo et al., 2011) which is due to the chromatin modifications on HOXD gene. This molecule interacts with lysine-specific demethylase 1 (LSD1), polycomb repressive complex 2 (PRC2), H3K27me3 (histone H3 tri-methylated at lysine 27) and H3K4me2 (histone H3 dimethyl Lys4) which eventually silences HOXD (Wu et al., 2010; Hajjari et al., 2015) (Fig. 3).

Another lncRNA is H19, which its overexpression plays a critical role in progress of cancers including CRC (Tian et al., 2016). H19 is involved in all stages of tumorigenesis (Raveh et al., 2015; Tian et al., 2016; Yang et al., 2017c). The responsible gene is a conserved and maternally expressed in vicinity of the IGF II gene locus, a maternally imprinted gene (Matouk et al., 2013a; Xie et al., 2016b). Explanations

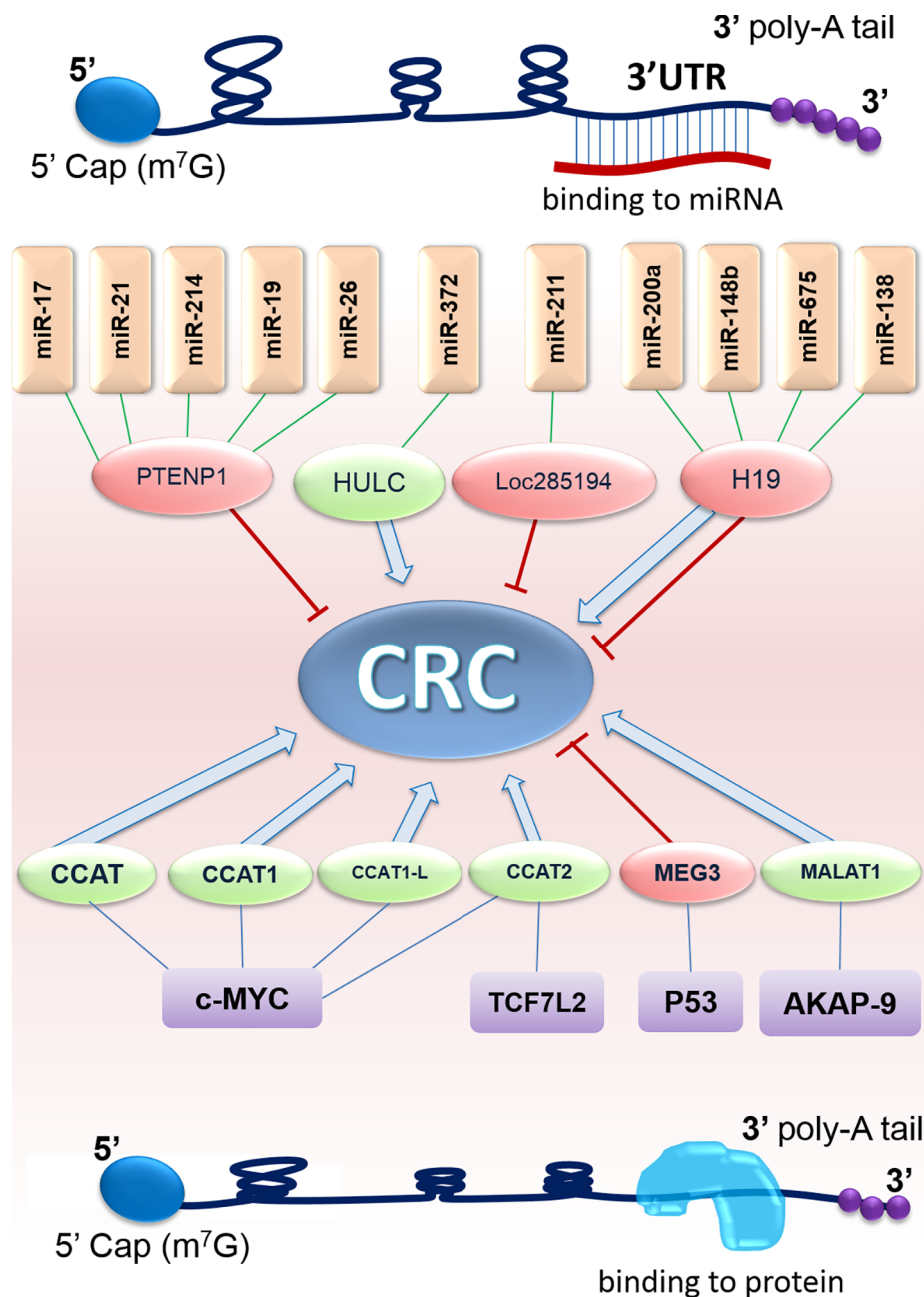


Fig. 4. A complex network of lncRNAs-miRNAs and lncRNAs-proteins interactions involved in progress or suppress of the CRC. As indicated, a number of lncRNAs-miRNAs interactions are involved in promotion or attenuation of the CRC (Upper part of the figure). Moreover, in CRC progress or prevention, several lncRNAs acts through interacting with proteins as shown at the lower part of the figure. For more detailed explanation please see the text.

on detailed molecular function of H19 functionality as an oncogene are arguable (Zhang et al., 2012a). For instance, H19 functions as an oncogene when acts as the precursor of miR-675. H19-derived miR-675 down-regulates tumor suppressor *Retinoblastoma (RB)* in human CRC cells (Baryte-Lovejoy et al., 2006). On the other hand c-Myc induced H19 could also promote the CRC. Despite the relevant information of H19 oncogenicity, some studies have demonstrated that H19 acts as a tumor suppressor in CRC at metastatic stage (Yoshimizu et al., 2008; Angrand et al., 2015).

A relevant lncRNA responsible for the suppression of CRC is maternally expressed gene 3 (MEG3) which is derived from DLK1-MEG3, an imprinted gene. Gene of this lncRNA is located on chromosome 14q32 (Zhou et al., 2012; Xie et al., 2016b). Suppressed expression of MEG3 is associated directly with the low histological grade, the enhanced tumor invasion, and the progressed tumor node metastatic

(TNM) CRC samples. Hence, MEG3 over-expression remarkably inhibits CRC cell proliferation due, which proposes a suitable therapeutic factor against CRC. It has been suggested that MEG3 releases p53 through targeting Mdm2 (Yin et al., 2015; Zhang et al., 2003; Zhou et al., 2007).

Prostate cancer-associated ncRNA transcripts 1 (PCAT-1) is considered as another lncRNA, which promotes of CRC. PCAT-1 was first identified to be involved in human prostate cancer development. Respective gene is located on the chromosome 8q24; in a distance of 725 kb upstream of the *c-Myc* oncogene. PCAT-1 is suppressed by PRC2 at normal condition, whereas increased expression of PCAT-1 is associated with CRC promotion and metastasis, with a direct correlation with the poor survival (Prensner et al., 2011; Ge et al., 2013).

Colon cancer-associated transcript 2 (CCAT2) which its gene is located on the chromosome 8q24.21 is another lncRNA which plays a critical role in tumorigenesis, through promoting chromosomal

instability (CIN) (Li et al., 2009; Ling et al., 2013). CCAT2 is over-expressed in CRC and promotes metastasis and tumor growth. Through binding to TCF7L2, a requisite TF in the WNT signaling pathway, CCAT2 increases WNT activity and *MYC* expression (Ling et al., 2013).

8. lncRNA interactions with miRNAs may be responsible for the promotion or suppression of CRC

Recently, the interaction between lncRNAs and RNA sequences has been more highlighted. lncRNAs can function as competing endogenous RNAs (ceRNAs), to change the essential biological functions of miRNAs, triggering deregulation in the expression levels of their target genes (Xie et al., 2016b). As an example high upregulation in liver cancer (HULC), a lncRNA which was first detected in the human hepatocellular carcinoma (HCC) tissues (Matouk et al., 2009), acts as miRNAs sponge. *HULC* gene is located on the 6p24.3 in human chromosome which comprises two exons (Panzitt et al., 2007). Enhanced expression level of *HULC* in CRC tissues at metastatic stage, is reported (Matouk et al., 2009). Having a poly-A tail with special binding site for miR-372, *HULC* prevents binding of miR-372 to target mRNAs (Xie et al., 2016c) (Fig. 4).

PTENP1 as a type of lncRNA, is a transcript of *PTEN* pseudogene, which is located on the chromosome 9q13.3. Several studies have indicated that PTENP1 which reduces cell proliferation, is down-regulated in CRC (Poliseno et al., 2010). It has been demonstrated that this lncRNA could able to sponge a variety of miRs including miR-17, miR-21, miR-214, miR-19, and miR-26 (Yang et al., 2017b) (Fig. 4).

Similarly, *Loc285194*, a tumor suppressor lncRNA is reported to be down-regulated in CRC in association with extensive tumor size, distant metastasis, the decreased disease-free survival, and the increased tumor stage (Qi et al., 2013). In normal condition, *Loc285194* represses the cell proliferation and induces apoptosis (Ding et al., 2015). This lncRNA contain two binding sites for miR-211. Direct transcriptional target of miR-211 is p53 (Liu et al., 2013) (Fig. 4).

H19 which was already described to perform as an epigenetic regulator, could also act as miRNA sponge in CRC (Liang et al., 2015). This lncRNA induces cell proliferation through competitively binding to miR-200a, thereby changing the β -catenin expression in CRC (Yang et al., 2017c). Also, H19 is reported to promote CRC metastasis by the negative modulation of miR-148b (Tian et al., 2016). Therefore, H19 could promote CRC development by acting as the ceRNA (Tsang et al., 2009). Contrarily, it has been shown that silencing H19 significantly increases the expression of miR-138 which was responsible for knock-down of *high-mobility group A1 (HMGA1)* transcripts, thereby promotes CRC invasion (Yang et al., 2017b) (Fig. 4).

9. lncRNAs interactions with proteins are also responsible for promotion or suppression of CRC

Several studies have reported that a number of CRC associated lncRNAs can interact with proteins, affecting the expression levels of the target genes (Xie et al., 2016c). Such lncRNAs are as follows:

MEG3, in which its overexpression could enhance notable increase in p53 protein levels in human cancer cells (Zhou et al., 2007; Pomerantz et al., 2009; Zhang et al., 2009). Other cases are CCAT isoforms, including CRC associated transcript 1 (CCAT1), CCAT1-the long isoform (CCAT1-L) and CRC associated transcript 2 (CCAT2). These lncRNAs control cell growth, metastasis and cell invasion. In addition, they are associated with c-Myc (Pomerantz et al., 2009; Sotelo et al., 2010; Kim et al., 2015; Yang et al., 2017e; Nissan et al., 2012; He et al., 2014; Alaiyan et al., 2013; He et al., 2014; Xiang et al., 2014; Ling et al., 2013).

The next lncRNA is MALAT1, with several biological functions like cell proliferation, cell migration and cell invasion in human CRC. MALAT-1 is over-expressed at early stage of CRC which stimulates tumor growth and promotes CRC development. MALAT1 regulates

PRKA kinase anchor protein 9 (AKAP-9), one of the genes involved in CRC cells, which is significantly upregulated at both mRNA and protein levels. Studies have demonstrated that MALAT1 can induce CRC tumor progression through its target protein AKAP-9 (Ji et al., 2003).

10. Conclusion

Since CRC is one of the most common human malignancies, understanding the molecular pathogenesis of this disease is very important and greatly contributes to the survival of patients with CRC. Enormous studies have shown that ncRNAs deregulation can effectively contribute to the promotion of CRC through diverse biological processes. In the present manuscript we tried to figure out the various contributions of ncRNAs. Understanding of these molecular mechanisms would be appropriate for further therapeutic strategies against CRC progress in human.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

The design of study was done by F.S.F., M.P. and K.G., Data mining was performed by M.E., M.K., and M.V., Interpretation of the obtained information was done by M.E., M.K., M.V., M.P., F.S.F., S.R.Z., S.I.G., M.H.N.E. and K.G., The manuscript was written by M.E., M.K., M.V., and approved by M.P., F.S.F., C.T.L., S.I.G., M.H.N.E. and K.G. and S.I.G. made critical reading and corrections. All authors read and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.gene.2020.144796>.

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