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REVIEW

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CRNDE: A Pivotal Oncogenic Long Non-Coding RNA in Cancers

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Colorectal Neoplasia Differentially Expressed (CRNDE), a long non-coding RNA that was initially identified as aberrantly expressed in colorectal cancer (CRC) has also been observed to exhibit elevated expression in various other human malignancies. Recent research has accumulated substantial evidence implicating CRNDE as an oncogenic player, exerting influence over critical cellular processes linked to cancer progression. Particularly, its regulatory interactions with microRNAs and proteins have been shown to modulate pathways that contribute to carcinogenesis and tumorigenesis. This review will comprehensively outline the roles of CRNDE in colorectal, liver, glioma, lung, cervical, gastric and prostate cancer, elucidating the mechanisms involved in modulating proliferation, apoptosis, migration, invasion, angiogenesis, and radio/chemoresistance. Furthermore, the review highlights CRNDE's potential as a multifaceted biomarker, owing to its presence in diverse biological samples and stable properties, thereby underscoring its diagnostic, therapeutic, and prognostic applications. This review aims to provide comprehensive insights of CRNDE-mediated oncogenesis and identify CRNDE as a promising target for future clinical interventions.

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Abbreviations: 5-Fu, 5-fluorouracil; ATAD2, ATPase family AAA domain-containing protein 2; BAD, Bcl-2-associated agonist of cell death; Bax, Bcl-2-associated X; BCAT1, Branched chain amino acid transaminase 1; Bcl-2, B-cell leukemia/lymphoma-2; CC, Cervical cancer; CCNB1, Cyclin B1; CCNE1, Cyclin E1; CDK6, Cyclin dependent kinase 6; CDNK1A, Cyclin dependent kinase inhibitor 1A; ceRNA, Competing endogenous RNA; circRNAs, Circular RNAs; COL5A1, Collagen alpha-1(V) chain; CRC, Colorectal cancer; CRNDE, Colorectal Neoplasia Differentially Expressed; DUSP5, Dual-specificity phosphatase 5; E2F3, E2F transcription factor 3; ECM, Extracellular matrix; EMT, Epithelial-mesenchymal transition; EZH2, Enhancer of zeste homolog 2; GLOBOCAN, World Health Organization's International Agency for Research on Cancer Global Cancer Observatory; HB, Hepatoblastoma; hnRNPUL2, Heterogeneous nuclear ribonucleoprotein U-like 2 proteins; HOTAIR, HOX transcript antisense RNA; IGF, insulin-like growth factor iPSCs, Human induced pluripotent stem cells; IRX5, Iroquois Homeobox 5; lncRNAs, Long non coding RNAs; MALAT 1, Metastasis-associated lung adenocarcinoma transcript 1; MARK2, Microtubule affinity-regulating kinase 2; miRNAs, MicroRNAs; MMPs, Matrix metalloproteinases; MS, Mass spectrometry; mTOR, Mammalian target of rapamycin signaling; ncRNAs, Non-coding RNAs; NSCLC, Non-small cell lung cancer; Nt., Nucleotides; ORF, Open reading frame; OXA, Oxaliplatin; PAK7, P21-activated kinases 7; PCNA, Proliferating cell nuclear antigen; PDK1, 3-phosphoinositide dependent protein kinase 1; PICALM, Phosphatidylinositol-binding clathrin assembly protein; PRC2, Polycomb Repressive Complex 2; PTX, Paclitaxel; PUMA, p53 upregulated modulator of apoptosis; PVT1, Plasmacytoma variant translocation 1; Rap1A, Ras-related protein 1A; Ras/MAPK, Ras/mitogen-activated protein kinase signaling pathway; rRNAs, Ribosomal RNAs; SRSF6, Serine and arginine rich splicing factor 6; SP1, Specificity protein 1; SYNE1, Spectrin Repeat Containing Nuclear Envelope Protein 1; TCF4, Transcription factor 4; TCF7L2, Transcription factor-like 2; TIMP-2, Tissue inhibitors of metalloproteinases 2; TMN stage, Tumor, node, metastasis stage; tRNAs, Transfer RNAs; VEGFA, Vascular endothelial growth factor A; Wnt2, Wnt family member 2; XIAP, X-linked inhibitor of apoptosis protein; ZEB1, Zinc finger E-box-binding homeobox 1.

Keywords: CRNDE, CRNDEP, long non-coding RNA, lncRNA, cancers, biomarkers

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INTRODUCTION

Cancer, one of the most common leading causes of premature mortality worldwide has a tremendous toll on the human population [1]. In 2018, the global cancer burden was estimated to increase by 18.1 million new cases and 9.6 million deaths [2]. The GLOBOCAN (World Health Organization's International Agency for Research on Cancer Global Cancer Observatory) predicts there will be an increase of 53.4% of new cancer cases worldwide by 2040, approximately 28.8 million each year [3]. While there are various etiological factors that may contribute to the development of cancer, regulation of genes and pathways at the molecular level still play a key role.

For over a decade, people have been confined to the central dogma of "DNA makes RNA makes protein," essentially relegating RNA to an intermediary role between genes and proteins [4]. During the transcription process, huge numbers of transcripts will be synthesized from the human genome [4]. However, the protein-coding mRNAs account for less than 2% of the transcripts and the remaining portion of the RNA transcripts are non-coding [4,5]. Therefore, researchers proposed that the overlooked non-coding RNAs (ncRNAs) might be associated with regulated transcription process observed in humans [6].

There are many different types of ncRNAs, microRNAs (miRNAs), circular RNAs (circRNAs), transfer RNAs (tRNAs), ribosomal RNAs (rRNAs) and long non coding RNAs (lncRNAs) are some of the functionally important examples [4,7]. Among these, lncRNAs is a class of ncRNAs that are ≥ 200 nucleotides (nt.) in transcription length and only have minimal or no protein-coding capacity due to the absence of an open reading frame (ORF) [8,9]. The lncRNAs have characteristics of poor sequence conservation across different species, are susceptible to the environment and their mode of action is diverse and complex [10].

Regardless of its protein-coding potential, lncRNAs still play a significant part in gene regulation [6]. In fact, lncRNAs participate in regulating the expression levels of their target genes at multiple levels, for instance, epigenetic, transcriptional, and post-transcriptional levels [6,10,11]. They work through diverse molecular regulatory mechanisms, such as participating in post-transcriptional process by interacting with miRNA or mRNA, affecting gene expression by inhibiting RNA polymerase II or chromatin remodeling, achieve localized regulation through transvection where the non-coding genes are able to regulate the expression of neighboring protein-coding genes [6,12-14].

Numerous studies have shown that dysregulation of lncRNAs is associated with the development and progression of a wide range of human diseases, especially in cancers. For example, lncRNA plasmacytoma variant translocation 1 (PVT1) was reported to promote cell proliferation in hepatoblastoma [15], lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT 1) enhances metastasis of lung cancer [16], lncRNA HOX transcript antisense RNA (HOTAIR) upregulates collagen alpha-1(V) chain (COL5A1) to enhance growth and metastasis through sponging miR-1277-5p [17].

In this review, lncRNA Colorectal Neoplasia Differentially Expressed (CRNDE) will be specifically discussed. First, an introduction to CRNDE, regarding its structure, biological effects and a nuclear peptide encoded by CRNDE will be provided. Next, the oncogenic role of CRNDE in various human cancers and the mechanism involved will be summarized. Lastly, the theoretical basis of CRNDE in future clinical applications will be discussed.

LncRNA CRNDE

The CRNDE gene, also known as LINC00180, CRNDEP, PNAS-108, lincIRX5, and NCRNA00180, is found on the long arm of chromosome 16, specifically at 16q12.2 [18]. It is located on the reverse strand and is believed to share a bidirectional promoter with the adjacent Iroquois Homeobox 5 (IRX5) gene found on the opposite strand [18] (Figure 1).

CRNDE comprises six exons, with five considered as core exons (E1, E2, and E4 to E6), while the remaining exon, E3, is less mentioned [10]. According to Ensembl database, to date, CRNDE was found to transcribe 30 transcript variants namely CRNDE-201 to CRNDE-230 most of them do not code for a protein [19]. Thus, due to its limited coding potential, CRNDE is classified as a lncRNA coding gene.

The expression of CRNDE is tissue-specific and biased expression can be seen in testis, lung, skin, fat, salivary gland, stomach, esophagus, heart, kidney, and prostate [18]. Expression of this locus is also found to increase in dividing tissues, notably in certain tumors such as colorectal adenomas and adenocarcinomas. Meanwhile, the insulin/insulin-like growth factor (IGF) can negatively regulate the transcript of CRNDE [18,19].

Biological Function of LncRNA CRNDE

CRNDE has been identified to act as a pivotal molecular switch for various biological processes such as tumorigenesis, gametogenesis, pluripotency, and differentiation [20].

The activity of CRNDE has the ability to regulate multilayered cellular processes that are associated with the hallmarks of cancer. For instance, it can facilitate cells to proliferate, differentiate, invade, and metastasize [21-

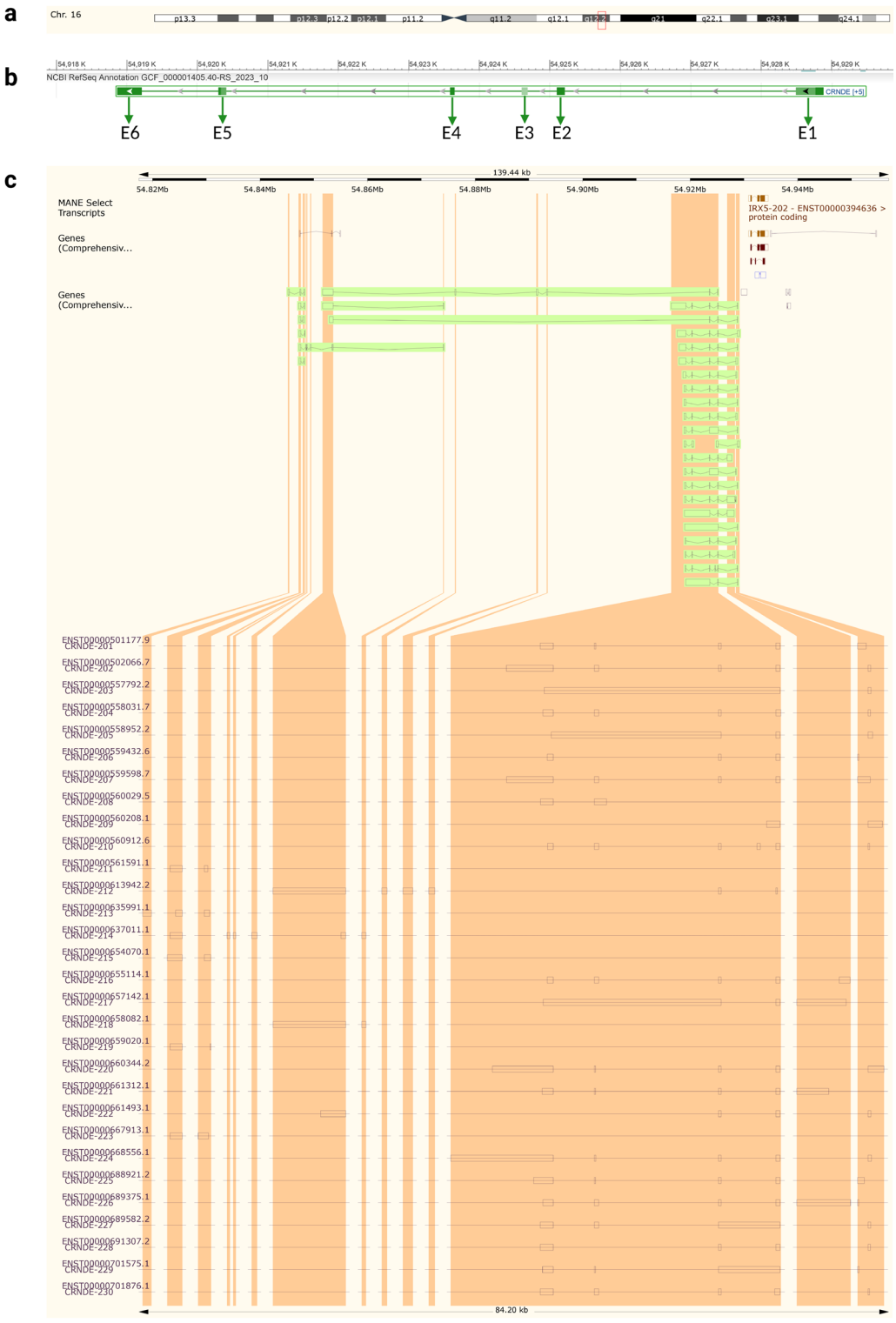

Figure 1. **a**. **Genomic locus of lncRNA CRNDE on Chromosome 16**. **b**. Exon (green bars with colored) and introns (green lines) are shown. The intensity of the green coloring of exon is proportional to the number of transcript variants that include a particular exon region. **c**. The identified splice variants of CRNDE are illustrated.

23]. Besides that, CRNDE can influence cytoskeletal dynamism and promote angiogenesis [20,24], yet it is able to suppress cell apoptosis and increase chemoresistance of cancer cells and tissues which increases tumor survival [22,25].

Additionally, CRNDE plays a crucial role in maintaining pluripotency of cells [26]. It exhibits the highest expression levels in early human development, specifically in the embryoid body and fetus. Subsequently, its expression gradually decreases during progress from the juvenile to adult stage [26]. Mouse CRNDE ortholog, known as linc1399, has also been identified as essential for maintaining the pluripotency of mouse embryonic stem cells and knockdown of CRNDE resulted in decreased levels of pluripotency markers [24]. These studies suggest that CRNDE is potentially involved in cancer development.

Although CRNDE is sometimes silenced or downregulated during cell differentiation, it was observed to be maintained or upregulated in certain specific cell lineages, thereby suggesting its role in cell differentiation [26]. For instance, CRNDE is highly expressed during the process of human induced pluripotent stem cells (iPSCs) differentiating into neurons [27].

Furthermore, the biased expression of CRNDE in testis cells and tissues generally suggests the role of CRNDE in gametogenesis [9,18]. Upon observation, CRNDE expression peaks during the meiosis stage, and remains relatively higher compared to its expression in other tissues even after spermatogenesis is complete [28]. For instance, a study showed that the CRNDE levels in human testicular samples that have no germ cell presence are 5.5-fold lower than in samples that contain spermatogonia [29].

CRNDEP, a Nuclear Micropeptide Encoded by CRNDE

According to Szafron et al., CRNDE does encode a nuclear peptide, namely CRNEDP [30]. CRNDEP is a micropeptide which consists of only 84 amino acids [30]. The findings show that CRNDEP expression level was increased in rapidly dividing tissues such as spermatocytes and squamous epithelium suggesting it may participate in cell turnover [30]. Besides that, CRNDEP was found to be able to stimulate the formation of stress granules and affect oxygen metabolism and cell proliferation regulation [30].

However, this statement conflicts with the "non-coding" characteristic of CRNDE which is claimed in many studies [30,31]. There are a few reasons that could explain this conflict. Firstly, the classification of lncRNAs is defined as sequences that are longer than 200 nt. with an ORF shorter than 100 amino acids [32]. Consequently, lncRNA may still consist of small ORFs enabling them to encode micropeptides [32]. In addition, conventional mass spectrometry (MS) is unable to detect micropeptides due to their physiochemical structure and low expression level that does not reach the MS peptide identification threshold [4]. Therefore, CRNDEP was hard to observe.

LncRNAs transcribed by RNA polymerase II are primarily processed insufficiently, resulting in diverse processing patterns [33]. Transcripts that are insufficient processed and contain intronic sequences will be retained in the nucleus, which is a characteristic of lncRNA [30,33]. Meanwhile, lncRNAs and mRNA that contain only exons will be exported to the cytoplasm, similar to protein-coding transcripts [30,33].

LncRNA CRNDE operates by influencing gene expression at various levels, including affecting chromatin structure and its function, modulating transcription of nearby and distant genes, and also altering RNA splicing, stability, and translation [33]. To give an example, LINC-PINT44 has the capability to attenuate cell proliferation and migration in lung and colon cancer. It achieves this by interacting with the Polycomb Repressive Complex 2 (PRC2) to suppress the gene-expression signature associated with cancer cell invasion [33].

On the other hand, lncRNA encoded peptide primarily functions through protein-protein interaction. For instance, LINC00961 encodes a peptide that is able to bind with actin-binding protein Spectrin Repeat Containing Nuclear Envelope Protein 1 (SYNE1), thereby promoting angiogenesis [34,35].

Given the evidence that Insulin/IGF negatively regulates CRNDE expression, studies have indicated that CRNDE intronic transcript can be suppressed by insulin/IGF through the PI3K/AKT/mTOR and Raf/MAPK signaling pathway. However, it was observed that overexpression of CRNDE nuclear transcript in colorectal cancer (CRC) has a reverse effect on this regulation. This results in an increase in glucose metabolism, lipid synthesis, and lactate secretion, facilitating aerobic glycolysis in cancer cells [36].

The discovery of this micropeptide revealed that the transcript of CRNDE may have divergent roles and capabilities as both lncRNA and protein-coding RNA in cells, and any imbalances between them may contribute to cancer development [30]. However, there have been limited studies focused on this area, and further research is needed to elucidate the roles of CRNDE transcripts in cells and the effects of their deregulation.

THE ROLES AND MECHANISMS OF LncRNA CRNDE IN VARIOUS CANCERS

The CRNDE was reported to act as a key player in the initiation and development of various types of cancers

in humans. This is clearly demonstrated by the LncRNA and Disease Database [37], which recorded the high correlation between CRNDE levels and cancers, such as CRC, stomach cancer, cervical cancer, breast cancer, gallbladder cancer, malignant glioma, renal cell carcinoma, pancreatic cancer, childhood medulloblastoma, and hepatoblastoma [37]. Herein, we will discuss some of the common cancers that correlate with elevated CRNDE expression.

Colorectal Cancer

CRC is the third most commonly diagnosed cancer worldwide but is the second leading cancer cause of death [38]. The significant upregulation of CRNDE in CRC was originally found in a database-mining analysis and the result has been demonstrated in both CRC cell lines and biopsy samples in other studies [39,40].

Jiang et al. revealed that CRNDE was able to form a functional complex with heterogeneous nuclear ribonucleoprotein U-like 2 proteins (hnRNPUL2) to direct the localization of hnRNPUL2 in the cytoplasm compartment [41]. The hnRNPUL2 accumulation in the cytoplasm increase CRNDE stability, thence resulting in a further increase of CRNDE expression [41]. Subsequently, the elevated expression of CRNDE promotes the cell cycling, cell proliferation, and metastasis of CRC cells both *in vitro* and *in vivo* through activating the Ras/mitogen-activated protein kinase (Ras/MAPK) signaling pathway [41].

Moreover, Ding et al. found that CRNDE expression in CRC tissues was positively correlated with the increase in tumor size and advancement of pathological stages [42]. Besides that, CRNDE achieves its cell proliferation role through epigenetically silencing the expression of dual-specificity phosphatase 5 (DUSP5) and cyclin dependent kinase inhibitor 1A (CDNK1A) transcription by binding with enhancer of zeste homolog 2 (EZH2) [42]. The direct binding of CRNDE on EZH2 inhibits the EZH2-mediated methylation modification [42]. Meanwhile, the knockdown of CRNDE *in vitro* and *in vivo* causes CRC cell proliferation to be arrested at the G1 stage and also promotes apoptosis [42,43].

On the other hand, CRNDE can function as a competing endogenous RNA (ceRNA) which can promote crosstalk with the target gene through the ceRNA/miRNA/mRNA regulatory network [44]. The mechanism for ceRNA is based on lncRNA competitively binding with miRNAs and preventing them from imposing their post-transcriptional regulation; thus, protecting mRNA from degradation and subsequently regulating the target gene expression [45].

Gao et al. reported that CRNDE acts as a ceRNA sponging miR-136 to promote metastasis by increasing expression of E2F transcription factor 1 (E2F1), a miR-136 targeted transcription factor that is responsible for cell cycle regulation, apoptosis, migration, and chemoresistance [40]. With a similar mechanism, Han et al. revealed that CRNDE repressed its target miR-181a-5p to prevent transcription factor 4 (TCF4) and β-catenin from being inhibited, thus modulating the activity of the Wnt/β-catenin signaling pathway to promote cell proliferation in CRC [46].

CRNDE is also able to enhance the Wnt/β-catenin signaling pathway and transcription factor-like 2 (TCF7L2) expression to promote cell proliferation, migration and invasion in CRC cells and tissues via competitively binding with miR-217 [43]. The main effector of the Wnt signaling pathway, β-catenin was found to be accumulated in the cytoplasm of CRNDE downregulated CRC cells [43]. Meanwhile, the accumulation can be reversed by overexpression of TCF7L2 since it is able to enhance the β-catenin nuclear translocation, consequently activating the Wnt/β-catenin signaling pathway for CRC tumorigenesis [43].

Liu et al. confirmed that upregulation of CRNDE promotes CRC progression by increasing cell proliferation, migration, invasion, and inhibiting apoptosis by sponging miR-126-5p to prevent it from repressing the expression of its target ATPase family AAA domain-containing protein 2 (ATAD2) [47]. Elevated CRNDE expression was found to promote lymph nodes metastasis in CRC since it is able to influence the expression levels of migration and invasion-related proteins such as E-cadherin, vimentin and matrix metalloproteinase (MMP) 9 [46,47].

Furthermore, CRC cells with high expression levels of CRNDE have demonstrated drug resistance characteristics against chemotherapy treatment [40,46,47]. It was reported that CRNDE knockdown decreased oxaliplatin (OXA) [40,46], Paclitaxel (PTX) [47] and 5-fluorouracil (5-Fu) [46] resistance in CRC cells. Figure 2 visually depicts the mechanisms of CRNDE in regulating the formation of CRC.

Liver Cancer

Liver cancer is ranked as the sixth highest incidence of cancer and accounts for the fourth most common cause of cancer death globally [38]. Highlighting some previous studies, tumor suppressing miRNAs including miR-217, miR-33a-5p, and miR-203 were negative targets of CRNDE. Therefore, elevated expression of CRNDE causes them to be lowly expressed in malignant liver cells and tissues. Figure 3a illustrates the regulatory roles of overexpressed CRNDE in liver cancer development.

Wang et al. proposed that CRNDE affects the mobility of hepatocellular carcinoma (HCC) cells through a miR-217/MAPK1 axis [48]. CRNDE overexpression and MAPK1 upregulation were found to positively regulate the epithelial-mesenchymal transition (EMT) protein

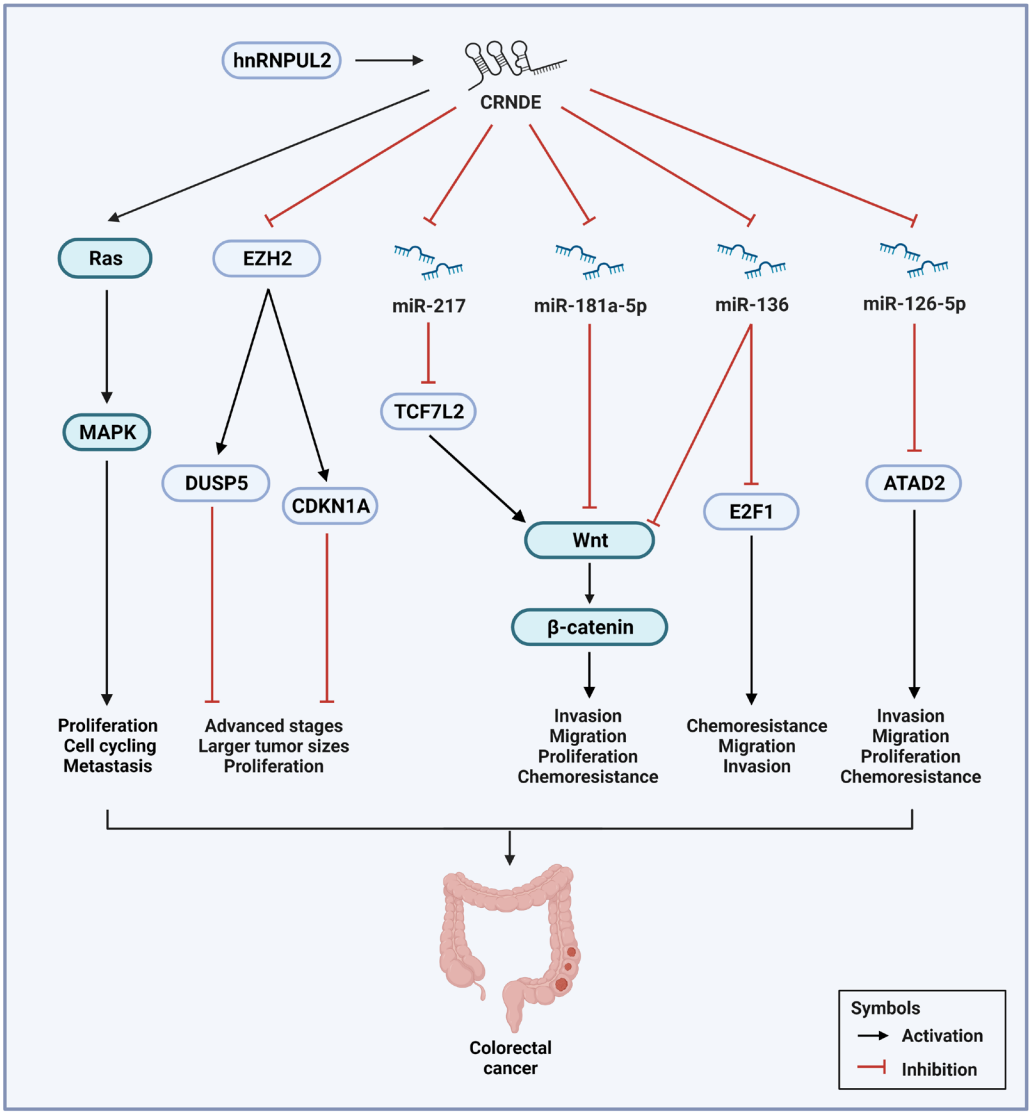

Figure 2. **The high expression level of CRNDE contributes to CRC by upregulating the signaling pathways such as Ras/MAPK, Wnt/β-catenin**. In addition, CRNDE is able to competitively bind to its miRNA targets: miR-217, miR-181a-5p, miR-136, and miR-126-5p to inhibit their regulatory activities. Meanwhile, CRNDE can bind to EZH2 to suppress the expression of DUSP5 and CDKN1A. Lastly, the accumulated cytoplasmic hnRNPUL2 can increase the stability of CRNDE. Created with BioRender.com.

markers, whereas miR-217 had the opposite effect [48]. As per observed, E-cadherin/Mucin-1 protein levels were found to be decreased and Vimentin/Fibronectin protein levels were found to be elevated, thus activating EMT to enhance proliferation, metastasis, and invasion in HCC cells [48]. Furthermore, CRNDE was also reported to contribute to radiation resistance in HCC by binding to specificity protein 1 (SP1) to modulate the transcription of downstream genes 3-phosphoinositide dependent protein kinase 1 (PDK1) [49].

Moreover, CRNDE is able to regulate miR-33a-5p and its target cyclin dependent kinase 6 (CDK6), hence contributing to HCC tumorigenesis [21]. The expression of CDK6 was found to be suppressed by CRNDE inhibition or miR-33a-5p overexpression and resulted in HCC cells arresting in the G0/G1 phase [21]. In addition, it was found that knockdown of CRNDE promoted apoptosis of HCC cells by affecting proteins associated with mitochondrial apoptosis, including Bcl-2-associated X (Bax), B-cell leukemia/lymphoma-2 (Bcl-2), caspase 3, and cytochrome-3 [21].

Furthermore, overexpression of CRNDE was also

found in human hepatoblastoma (HB), the most common primary malignancy in infancy and childhood [50]. The knockdown of CRNDE was found to suppress HB tumor growth and tumor angiogenesis *in vivo*, whereas reducing cell viability, proliferation, migration, and angiogenic effects were demonstrated *in vitro* [51,52]. Chen et al. suggested CRNDE could accelerate the development of HB through regulating vascular endothelial growth factor A (VEGFA) expression or mammalian target of rapamycin (mTOR) signaling [51,52]. The results proved that CRNDE expression level was correlated with the tumor stages and able to promote angiogenesis by downregulating the tumor suppressor miR-203, which is able to inhibit angiogenesis, suppress cell viability, migration, and angiogenesis by regulating VEGFA expression [52].

Glioma

Glioma, which arises in the glial tissue and primarily occurs in the brain, is a malignancy that has a high recurrence and mortality rate [53]. Yet, it is the most prevalent type of primary intracranial tumor which accounts for approximately 81% of malignant brain conditions [54]. According to the latest revision in 2016 by WHO, glioma is classified into WHO I-IV grades based on malignant behavior [55].

Under normal conditions, miR-186 negatively represses the X-linked inhibitor of apoptosis protein (XIAP), a potent anti-apoptotic protein, and P21-activated kinases 7 (PAK7), an important regulator of diverse oncogenic signaling pathway [56-58]. Zheng et al. showed that CRNDE negatively regulated miR-186 through direct binding to prevent XIAP and PAK7 and their downstream proteins, including caspase-3, microtubule affinity-regulating kinase 2 (MARK2), Bcl-2-associated agonist of cell death (BAD), and cyclin D1 from being inhibited, resulting in enhanced cell proliferation, migration, invasion concomitant with inhibited cell apoptosis in glioma [57].

Moreover, Li et al. have reported that CRNDE negatively regulates miR-136-5p to protect Bcl-2 and Wnt2 from miR-136-5p-mediated inhibition, which in turn activates the PI3K/Akt/mTOR signaling pathway [59]. Bcl-2 is a key regulator of the suppressor gene and apoptosis suppressor factor, while Wnt2 is a crucial activator for cell proliferation, development, and differentiation [60,61]. Thereby, CRNDE serves as ceRNA for miR-136-5p to inhibit its post-transcriptional repression ability and subsequently upregulates Bcl-2 and Wnt2 that promote glioma progression [59]. Figure 3b illustrates the connection between CRNDE and the formation of glioma.

Lung Cancer

Altogether, lung cancer is the leading cause of cancer incidence and mortality globally [38]. The expression of CRNDE is also elevated in non-small cell lung cancer (NSCLC). The oncogenic roles of CRNDE in NSCLCs are to promote cell proliferation and growth, inhibit apoptosis, and induce tumor proliferation *in vivo* [62,63].

Fan et al. stated that the knockdown of CRNDE suppressed cell proliferation and enhanced the apoptosis of NSCLC cells. The study reported that miR-641, a tumor suppressor in NSCLC was repressed due to the direct binding of CRNDE to it [62,64]. The CDK6, which plays a pivotal role in response to growth factors and mitogenic stimuli in the G1 phase [65] was negatively regulated by miR-641. Thus, the upregulation of CRNDE in NSCLC that repressed miR-641 in turn causes the increase in CDK6 expression, which contributes to proliferation and inhibits apoptosis in NSCLC cells [62].

Consistent with previous findings, Liu et al. found that through activating the PI3K/Akt pathway, CRNDE was able to promote cell proliferation and growth of NSCLC both *in vitro* and *in vivo.* The positive correlations between cyclins CDK4, CDK6, and cyclin E1 (CCNE1) and CRNDE suggest CRNDE can regulate the cell cycle through the PI3K/Akt pathway. The upregulation of CRNDE could induce the PI3K/Akt pathway to enhance cell proliferation and growth *in vitro* and promote tumor formation *in vitro* [63]. Figure 4a demonstrates the roles of CRNDE in the development of NSCLC.

Cervical Cancer

CRNDE is present in an upregulated manner in various malignant cells and tissues, including cervical cancer (CC). Today, CC is the fourth most common gynecological cancer [38]. The overexpression of CRNDE was reported to markedly enhance cervical cancer cell growth and progression through diverse mechanisms, for instance, modulating the miR-183/CCNB1 axis [8], regulating the expression of PUMA [66] and targeting the miR-4262/ZEB1 axis to affect Wnt/β-catenin pathway [67].

CRNDE contributes to CC cell growth by sponging miR-183 to activate cyclin B1 (CCNB1) expression [8]. Bai et al. showed *in vitro* silencing of CRNDE led to attenuation of CC progression by markedly decreased expression of cyclin D1 and N-cadherin with significantly increased levels of tissue inhibitors of metalloproteinases 2 (TIMP-2) and caspase-3, suggesting CRNDE has a functional role in regulating cell proliferation and apoptosis in CC [8]. Next, Ren et al. confirmed that CRNDE was able to achieve the same effects by inhibiting miR-4262 to increase zinc finger E-box-binding homeobox 1 (ZEB1) expression and activate the Wnt/β-catenin pathway [67]. It was shown that expression of proteins such as Ki-67 and proliferating cell nuclear antigen (PCNA) that are related to cell proliferation and Bcl-2 which is an anti-apop-

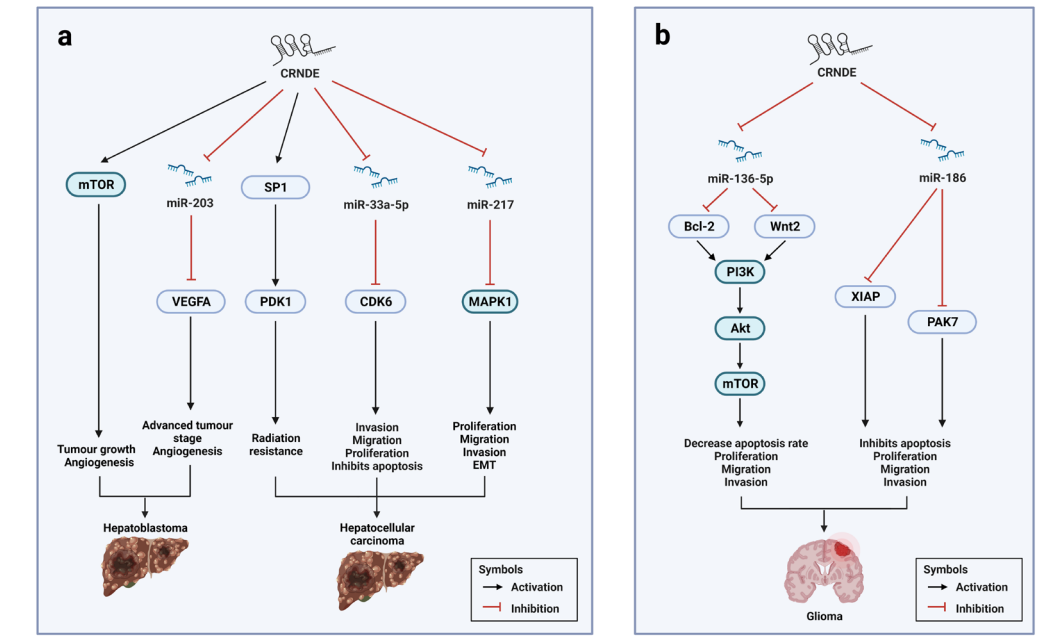

Figure 3. **a**. **Overexpression of CRNDE involved in liver cancer development through repressing its negative targets** such as miR-217, miR-33a-5p, and miR-203, subsequently upregulates the expression of MAPK1 and downstream targets: CDK6, BCAT1 and VEGFA. **b**. CRNDE promotes glioma through negative regulation of miR-136-5p and miR-186. Created with BioRender.com.

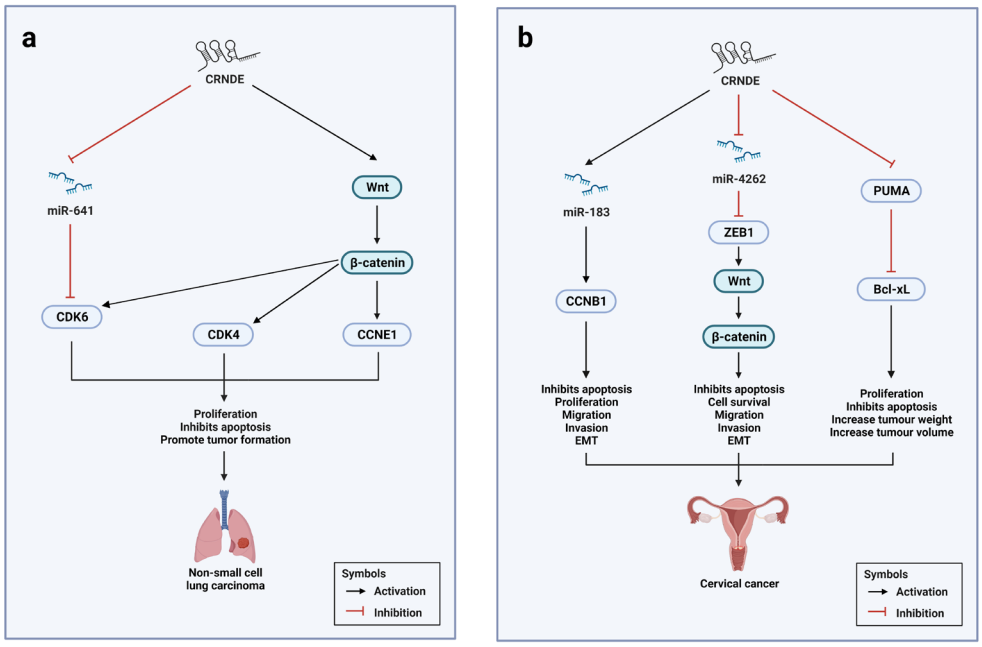

Figure 4. **a**. **CRNDE contributes to NSCLC by activating PI3K/Akt pathway**. CRNDE function as a ceRNA targeting miR-641 to modulate CDK6. **b**. CRNDE enhances the progression of cervical cancer through negative modulating miR-183/CCNB1 axis, regulating expression of PUMA and targeting miR-4262/ZEB1 axis to affects Wnt/β-catenin pathway. Created with BioRender.com.

totic protein were decreased together with an increased expression of pro-apoptotic protein Bax in CRNDE knockdown [67]. In addition, E-cadherin, N-cadherin, Vimentin, and Snail were also the downstream proteins of ZEB1 and hence via targeting miR-4262, CRNDE was able to participate in cell migration, invasion, and EMT in CC cancer tumors [67].

Yu et al. found that the p53 upregulated modulator of apoptosis (PUMA) was suppressed by CRNDE through direct binding to enhance CC progression [66]. PUMA, a critical mediator that supports p53 to accomplish its apoptotic effect, was found essential in suppressing various tumor progression [68]. PUMA functions by interacting with anti-apoptotic molecules, Bcl-xL, causing it to unfold partially internally, thus leading to apoptosis in CC cells [69]. The findings of an *in vivo* study using mice in which CRNDE was knocked down showed a noticeably reduced tumor weight and volume, which indicated the decreased cell proliferation ability in CC tumors [8,66]. This confirms the role of CRNDE as an oncogene in CC that is able to regulate cell growth, migration, invasion, apoptosis, and EMT events [8,66]. Figure 4b elucidates how CRNDE contributes to the development of CC.

Gastric Cancer

Gastric cancer is the third leading cause of cancer mortality and ranks fifth in terms of cancer incidence [38]. Recently, the upregulation of CRNDE was reported to play a key role in gastric cancer tumorigenesis through modulating the miR-145/E2F3 axis or regulating PI3K/Akt pathway [70,71]. Conversely, there is another study reported that low expression levels of CRNDE may lead to drug resistance in gastric cancer cells and tissues [72]. Figure 5a illustrates the role of CRNDE in the formation of gastric cancer.

CRNDE acts as a molecular sponge to negatively regulate the expression level of miR-145 to increase E2F transcription factor 3 (E2F3) expression [71]. Overexpression of CRNDE in gastric cancer will increase cell viability and promote cell proliferation and colony formation significantly [71]. Furthermore, high expression of CRNDE was associated with invasion depth, lymph node metastasis, tumor, node, metastasis (TMN) stage, and shorter overall survival in gastric cancer patients [70]. CRNDE achieved these oncogenic effects by affecting the PI3K/Akt pathway [70].

Interestingly, Zhang et al. demonstrated that downregulated CRNDE expression will result in chemoresistance and low sensitivity to chemotherapy in gastric cancer cells [72]. The study suggested CRNDE controls the autophagy mediated chemoresistance activity by direct binding to serine and arginine rich splicing factor 6 (SRSF6) and reduces its protein stability, which in turn results in reduced alternative splicing events. SRSF6 is a splicing factor that is involved in the regulation of cell chemotherapy resistance. It was shown that the sensitivity of MGC803 cells to oxaliplatin and 5-FU was markedly increased when the expression of SRSF6 is decreased *in vitro* and *in vivo* [72]. This can be explained by the significant L-to-S isoform switch of phosphatidylinositol-binding clathrin assembly protein (PICALM) RNA when SRSF6 is depleted, and the overexpression of PICALMS enhances the chemosensitivity properties of gastric cancer cells [72].

Prostate Cancer

According to GLOBOCAN 2018, prostate cancer is the second most diagnosed cancer amongst males worldwide [38]. In prostate cancer, CRNDE functions to promote cell proliferation by inhibiting apoptosis and enhancing cell migration and invasion through modulating the expression level of microRNA such as miR-146a-5p and miR-101 [73,74]. Figure 5b shows how the CRNDE is involved in the development of prostate cancer.

Fu et al. proposed that CRNDE inhibits apoptosis and contributes to the proliferation and metastasis of prostate cancer by regulating its direct target miR-146a-5p [73]. The study found that expression of MMP-2 and MMP-9, which play crucial roles in extracellular matrix (ECM) degradation and angiogenesis was decreased when CRNDE is downregulated, hence inhibiting invasion and migration of prostate cancer cells [73,75]. Next, Chen et al. reported that CRNDE influenced prostate cancer progression by preventing miR-101 from suppressing its target oncogene, Ras-related protein 1A (Rap1A) [74]. Therefore, CRNDE possibly advanced prostate cancer progression through sponging miR-101 to increase Rap1A expression [74].

LncRNA CRNDE IN FUTURE CLINICAL APPLICATION

At present, tumor biopsy, imaging, and endoscopy are the commonly performed conventional diagnostic methods for cancers. However, the process of these methods may possess certain degree of risk and discomfort to patients. Furthermore, they can have a high false negative result rates [76]. Thus, research for a novel non-invasive molecular biomarker that have high accuracy should be pursued.

Studies reported that lncRNAs are detectable in nearly all body fluids and tissues such as peripheral blood components, serum, and plasma [77,78]. In addition, lncRNAs are quite stable and have a strong resistance toward degradation by RNases [78]. This has greatly eased the detection process using RT-qPCR [79]. Therefore, CRNDE as a lncRNA, may have the potential to be a more accurate and effective diagnostic biomarker than

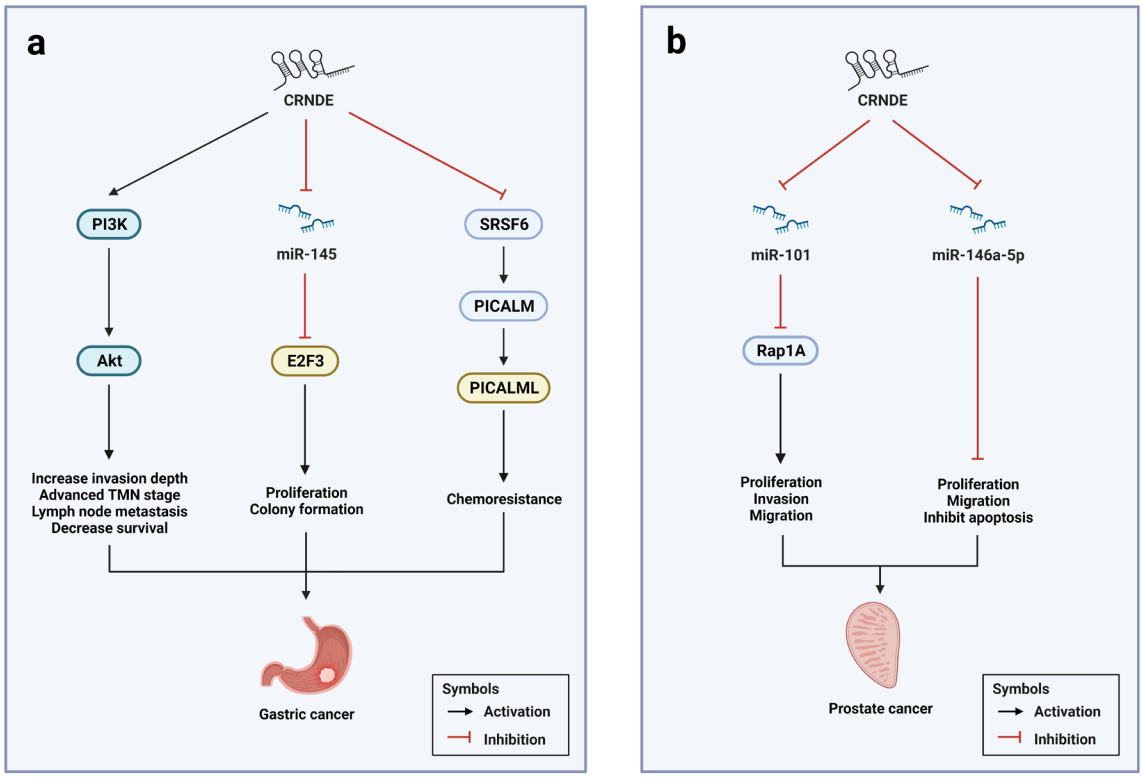

Figure 5. **a**. **CRNDE mediated the important PI3K/Akt signaling pathway to promote the development of gastric cancer**. The high expression level of CRNDE can bind to SRSF6 to reduce its protein stability, hence regulating its downstream target PICALM to affect the chemosensitivity of GC cells. **b**. CRNDE acts as an oncogenic lncRNA to significantly enhance the development of prostate cancer through negatively modulating miR-146a-5p and miR-101/Rap1A axis. Created with BioRender.com.

protein, protein-coding RNAs, and DNA.

Mounting evidence has displayed there is a significant correlation of CRNDE overexpression with clinicopathologic features such as tumor size and weight [8,38], differentiation of primary tumor [80], invasion depth of primary focus [80], involvement of lymph nodes metastasis [80,81], and advanced TMN stage [82]. Additionally, elevated CRNDE expression levels predict an unfavorable prognosis for cancers characterized by poorer overall survival, an increased chance of recurrence, and a shorter time for recurrence [80,82].

For example, the CRNDE isoforms, CRNDE-h and CRNDE-p, demonstrated a highly elevated expression pattern in the serum of CRC patients [83-85]. Patients who were associated with factors of poor clinical outcome were found to have high levels of exosomal serum CRNDE-h levels [83,84]. Meanwhile, advanced clinical staging (stage III or IV), higher tumor classification (T3 or T4) and lymph node involvement and distant metastasis were reported to be associated with high CRNDE-p serum exosomal levels [83,85].

Generally, lncRNAs are expressed at a low level in a healthy individual, but their deregulation in either up- or down-regulated expression is commonly seen during cancers [86]. Hence, the aberrant expression and biological function of CRNDE in various human cancers has provided a convincing theoretical basis that CRNDE may be a therapeutic target for cancer treatment (Table 1). Moreover, the disease specific expression manner gives CRNDE the capability to be developed as a vital target of therapy to achieve selective killing of cancer cells and avoid toxicities to other cells [86].

Overall, CRNDE demonstrates great potential to be a molecular biomarker for diagnosis, prognosis, and a therapeutic target in different types of cancers. An effective molecular biomarker not only helps physicians provide tailored cancer treatment for cancer patients but is also able to support disease progress monitoring. Thus, better care prevention and treatment can be delivered.

CONCLUSION

CRNDE, as a pivotal lncRNA that is abnormally expressed in many different cancers. It is found to be in-

Table 1. The Expression Pattern of CRNDE, Involved Protein or DNA and its Functional Roles in Different Human Cancers

Functional roles	Type of cancers	CRNDE expression	Interaction with protein or DNA	Pathway involved	Cell lines involved	References
Proliferation	CRC	Upregulated	hnRNPUL2, DUSP5/CDNK1A, miR-217/ TCF7L2, miR-181a-5p, miR-126-5p/ ATAD2 axis	Ras/MAPK pathway, Wnt/β-catenin pathway	HCT-116, Caco2, DLD1, SW480, SW620, LS174T	[41-43,46,47]
	HCC	Upregulated	miR-217/MAPK1 axis, miR-33a-5p/CDK6 axis	-	HepG2, Huh-6, Huh-7	[21]
	HB	Upregulated	miR-203/VEGFA axis	-	HepG2, HuH-6	[51,52]
	Glioma	Upregulated	miR-186, XIAP, PAK7, miR-136-5p, Bcl-2, Wnt2	PI3K/Akt/mTOR pathway	GSC-U87, GSC-U251	[57]
	Lung cancer	Upregulated	miR-641/CDK6 axis	PI3K/Akt pathway	H1299, SPC-A1, A549, PC-9, SK-MES-1	[62,63]
	Cervical cancer	Upregulated	miR-183/CCNB1 axis, PUMA, miR-4262/ ZEB1 axis	Wnt/β-catenin pathway	SiHa cells, Caski cells, HeLa cells	[8,67]
	Gastric cancer	Upregulated	miR-145/E2F3 axis	PI3K/Akt pathway	SGC-7901, BGC-823, MGC-803, MNK-45	[70,71]
	Prostate cancer	Upregulated	miR-146a-5p, miR-101/Rap1A	-	PC3, 22RV1	[73,74]
Invasion	CRC	Upregulated	miR-136/ E2F1, hnRNPUL2, miR-217/ TCF7L2, miR-126-5p/ATAD2 axis	Ras/MAPK pathway, Wnt/β-catenin pathway	HCT-116, Caco2, SW480, SW620 DLD1, LS174T	[40,43,47]
	HCC	Upregulated	miR-217/MAPK1 axis, miR-33a-5p/CDK6 axis	-	HepG2, Huh-7	[21,48]
	Glioma	Upregulated	miR-186, XIAP, PAK7, miR-136-5p, Bcl-2, Wnt2	PI3K/Akt/mTOR pathway	GSC-U87, GSC-U251	[57,59]
	Cervical cancer	Upregulated	miR-183/CCNB1 axis, miR-4262/ZEB1 axis	Wnt/β-catenin pathway	SiHa cells, Caski cells, HeLa cells	[8,67]
	Gastric cancer	Upregulated	-	PI3K/Akt pathway	MGC-803, MNK-45	[70]
	Prostate cancer	Upregulated	miR-146a-5p, miR-101/Rap1A	-	PC3, 22RV1	[73,74]
Migration	CRC	Upregulated	miR-136/ E2F1, hnRNPUL2, miR-217/ TCF7L2, miR-126-5p/ATAD2 axis	Ras/MAPK pathway, Wnt/β-catenin pathway	HCT-116, Caco2, SW480, SW620, DLD1, LS174T	[40,41,43,47]
	HCC	Upregulated	miR-217/MAPK1 axis, miR-33a-5p/CDK6 axis	-	HepG2, Huh-7	[21,48]

	Glioma	Upregulated	miR-186, XIAP, PAK7, miR-136-5p, Bcl-2, Wnt2	PI3K/Akt/mTOR pathway	GSC-U87, GSC-U251	[57,59]
	Cervical cancer	Upregulated	miR-183/CCNB1 axis, miR-4262/ZEB1 axis	Wnt/β-catenin pathway	SiHa cells, Caski cells, HeLa cells	[8,67]
	Gastric cancer	Upregulated	-	PI3K/Akt pathway	MGC-803, MNK-45	[70]
	Prostate cancer	Upregulated	miR-146a-5p, miR-101/Rap1A	-	PC3, 22RV1	[73,74]
Apoptosis	CRC	Upregulated	DUSP5/CDKN1A, miR-126-5p/ATAD2 axis	-	DLD1, HCT116, SW480, SW620	[42,47]
	HCC	Upregulated	miR-33a-5p/CDK6 axis	-	Huh-7	[21]
	Glioma	Upregulated	miR-186, XIAP, PAK7, miR-136-5p, Bcl-2, Wnt2	PI3K/Akt/mTOR pathway	GSC-U87, GSC-U251	[57,59]
	Lung cancer	Upregulated	miR-641/CDK6 axis	-	H1299, SPC-A1	[62]
	Cervical cancer	Upregulated	miR-183/CCNB1 axis, miR-4262/ZEB1 axis	Wnt/β-catenin pathway	SiHa cells, Caski cells, HeLa cells	[8,67]
	Prostate cancer	Upregulated	miR-146a-5p, miR-101/Rap1A	-	PC3, 22RV1	[73,74]
Angiogenesis	HB	Upregulated	miR-203/VEGFA axis	-	HuH-6, HepG2	[51,52]
Chemoresistance	CRC	Upregulated	miR-136, miR-181a-5p, miR-126-5p/ATAD2	Wnt/β-catenin pathway	SW480, SW620, HCT116	[39,40,46,47]
	Gastric cancer	Downregulated	SRSF6, PICALM	-	MGC-803	[69]
Radiation resistance	HCC	Upregulated	SP1/PDK1 axis	-	Huh7R, SNU-387R	[26]

volved in regulating cell proliferation, metastasis, apoptosis, radiosensitivity, and chemoresistance in cancer cells and tissues. Cancer patients with highly elevated CRNDE expression showed poor prognosis with aggressive clinicopathologic features such as larger tumor size, advanced TMN stage, distant metastasis, and worse lymph node metastasis.

While the research studies have shed light on the oncogenic roles of lncRNA CRNDE in various cancer types, it is crucial to recognize that the interactions between CRNDE and cellular processes are intricate. The majority of studies focus on transcriptional levels and the pathological mechanisms remain unclear, leaving a rich area for further investigation.

Furthermore, it is important to acknowledge that signaling pathways can often be mediated by other factors such as protein-protein interaction. However, the ability to dissect the contributions of CRNDE in cancer and precisely pinpoint causal relationships is still a limitation in the field.

Often identification of lncRNAs can be challenging, given their structural similarity with mRNA and their loose classification as transcribed RNA molecules that are longer than 200 nucleotides that do not encode proteins. Growing evidence shows that some lncRNAs possess protein-coding abilities and play functional roles in cellular processes. This prompts us to consider a more precise definition of lncRNAs, particularly those with the potential to code for proteins.

REFERENCES

1. Soerjomataram I, Bray F. Planning for tomorrow: global cancer incidence and the role of prevention 2020-2070. Nat Rev Clin Oncol. 2021 Oct;18(10):663–72.
2. Hulvat MC. Cancer Incidence and Trends. Surg Clin North Am. 2020 Jun;100(3):469–81.
3. Global Cancer Observatory. Cancer Tomorrow [cited 2021 Aug 19]. Available from: https://gco.iarc.fr/tomorrow/en
4. Ye M, Zhang J, Wei M, Liu B, Dong K. Emerging role of long noncoding RNA-encoded micropeptides in cancer. Cancer Cell Int. 2020;20:506-. https://doi.org/10.1186/s12935-020-01589-x.
5. Yao RW, Wang Y, Chen LL. Cellular functions of long noncoding RNAs. Nat Cell Biol. 2019 May;21(5):542–51.
6. Mercer TR, Dinger ME, Mattick JS. Long non-coding RNAs: insights into functions. Nat Rev Genet. 2009 Mar;10(3):155–9.
7. Mattick JS, Makunin IV. Non-coding RNA. Hum Mol Genet. 2006 Apr;15(Spec No 1 suppl_1):R17–29.
8. Bai X, Wang W, Zhao P, Wen J, Guo X, Shen T, et al. LncRNA CRNDE acts as an oncogene in cervical cancer through sponging miR-183 to regulate CCNB1 expression. Carcinogenesis. 2020 Mar;41(1):111–21.
9. Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, Tilgner H, et al. The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. Genome Res. 2012 Sep;22(9):1775–89.
10. Dai M, Li S, Qin X. Colorectal neoplasia differentially expressed: a long noncoding RNA with an imperative role in cancer. OncoTargets Ther. 2018 Jun;11:3755–63.
11. Lu Y, Sha H, Sun X, Zhang Y, Wu Y, Zhang J, et al. CRNDE: an oncogenic long non-coding RNA in cancers. Cancer Cell Int. 2020;20:162-. https://doi.org/10.1186/s12935-020-01246-3.
12. Kino T, Hurt DE, Ichijo T, Nader N, Chrousos GP. Noncoding RNA gas5 is a growth arrest- and starvation-associated repressor of the glucocorticoid receptor. Sci Signal. 2010;3(107):ra8-ra. https://doi.org/10.1126/scisignal.2000568.
13. Liu Y, Sharma S, Watabe K. Roles of lncRNA in breast cancer. Front Biosci (Schol Ed). 2015 Jun;7(1):94–108.
14. Mattick JS, Gagen MJ. The evolution of controlled multitasked gene networks: the role of introns and other noncoding RNAs in the development of complex organisms. Mol Biol Evol. 2001 Sep;18(9):1611–30.
15. Luo Z, Cao P. Long noncoding RNA PVT1 promotes hepatoblastoma cell proliferation through activating STAT3. Cancer Manag Res. 2019 Sep;11:8517–27.
16. Gutschner T, Hämmerle M, Eissmann M, Hsu J, Kim Y, Hung G, et al. The noncoding RNA MALAT1 is a critical regulator of the metastasis phenotype of lung cancer cells. Cancer Res. 2013 Feb;73(3):1180–9.
17. Wei Z, Chen L, Meng L, Han W, Huang L, Xu A. LncRNA HOTAIR promotes the growth and metastasis of gastric cancer by sponging miR-1277-5p and upregulating COL5A1. Gastric Cancer. 2020 Nov;23(6):1018–32.
18. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information - Gene [Internet]. 2004- [cited 2021 Aug 22]. Available from: https://www.ncbi.nlm.nih.gov/gene/?term=643911#variation
19. Howe KL, Achuthan P, Allen J, Allen J, Alvarez-Jarreta J, Amode MR, et al. Ensembl 2021. Nucleic Acids Res. 2021 Jan;49 D1:D884–91.
20. Zhou Y, Wang R, Xu T, Xie P, Zhang Y, Zhang A, et al. Prognostic Value of Long Noncoding RNA CRNDE as a Novel Biomarker in Solid Cancers: An Updated Systematic Review and Meta-Analysis. J Cancer. 2019 May;10(11):2386–96.
21. Lin C, Xiang Y, Sheng J, Liu S, Cui M, Zhang X. Long non-coding RNA CRNDE promotes malignant progression of hepatocellular carcinoma through the miR-33a-5p/CDK6 axis. J Physiol Biochem. 2020 Aug;76(3):469–81.
22. Xie S-C, Zhang J-Q, Jiang X-L, Hua Y-Y, Xie S-W, Qin Y-A, et al. LncRNA CRNDE facilitates epigenetic suppression of CELF2 and LATS2 to promote proliferation, migration and chemoresistance in hepatocellular carcinoma. Cell Death Dis. 2020;11(8):676-. https://doi.org/10.1038/s41419-020-02853-8.
23. Ding Q, Mo F, Cai X, Zhang W, Wang J, Yang S, et al. LncRNA CRNDE is activated by SP1 and promotes osteosarcoma proliferation, invasion, and epithelial-mesenchymal transition via Wnt/β-catenin signaling pathway. J Cell Biochem. 2020 Jun;121(5-6):3358–71.
24. Zhao J, Li L, Han ZY, Wang ZX, Qin LX. Long noncoding RNAs, emerging and versatile regulators of tumor-induced

angiogenesis. Am J Cancer Res. 2019;9(7):1367-81. Epub 20190701.
25. Sun XH, Fan WJ, An ZJ, Sun Y. Inhibition of Long Noncoding RNA CRNDE Increases Chemosensitivity of Medulloblastoma Cells by Targeting miR-29c-3p. Oncol Res. 2020 Feb;28(1):95–102.
26. Ellis BC, Molloy PL, Graham LD. CRNDE: A Long Non-Coding RNA Involved in CanceR, Neurobiology, and DEvelopment. Front Genet. 2012;3:270-. https://doi.org/10.3389/fgene.2012.00270.
27. Lin M, Pedrosa E, Shah A, Hrabovsky A, Maqbool S, Zheng D, et al. RNA-Seq of human neurons derived from iPS cells reveals candidate long non-coding RNAs involved in neurogenesis and neuropsychiatric disorders. PLoS One. 2011;6(9):e23356-e. Epub 2011/09/07. https://doi.org/10.1371/journal.pone.0023356.
28. Fratta E, Coral S, Covre A, Parisi G, Colizzi F, Danielli R, et al. The biology of cancer testis antigens: putative function, regulation and therapeutic potential. Mol Oncol. 2011 Apr;5(2):164–82.
29. von Kopylow K, Kirchhoff C, Jezek D, Schulze W, Feig C, Primig M, et al. Screening for biomarkers of spermatogonia within the human testis: a whole genome approach. Hum Reprod. 2010 May;25(5):1104–12.
30. Szafron LM, Balcerak A, Grzybowska EA, Pienkowska-Grela B, Felisiak-Golabek A, Podgorska A, et al. The Novel Gene CRNDE Encodes a Nuclear Peptide (CRNDEP) Which Is Overexpressed in Highly Proliferating Tissues. PLoS One. 2015;10(5):e0127475-e. https://doi.org/10.1371/journal.pone.0127475.
31. Young RS, Ponting CP. Identification and function of long non-coding RNAs. Essays Biochem. 2013;54:113–26.
32. Chen LL, Carmichael GG. Long noncoding RNAs in mammalian cells: what, where, and why? Wiley Interdiscip Rev RNA. 2010;1(1):2–21.
33. Statello L, Guo CJ, Chen LL, Huarte M. Gene regulation by long non-coding RNAs and its biological functions. Nat Rev Mol Cell Biol. 2021 Feb;22(2):96–118.
34. Xing J, Liu H, Jiang W, Wang L. LncRNA-Encoded Peptide: Functions and Predicting Methods. Front Oncol. 2020;10:622294. Epub 20210114. https://doi.org/10.3389/fonc.2020.622294.
35. Spencer HL, Sanders R, Boulberdaa M, Meloni M, Cochrane A, Spiroski AM, et al. The LINC00961 transcript and its encoded micropeptide, small regulatory polypeptide of amino acid response, regulate endothelial cell function. Cardiovasc Res. 2020 Oct;116(12):1981–94.
36. Ellis BC, Graham LD, Molloy PL. CRNDE, a long non-coding RNA responsive to insulin/IGF signaling, regulates genes involved in central metabolism. Biochim Biophys Acta. 2014 Feb;1843(2):372–86.
37. Bao Z, Yang Z, Huang Z, Zhou Y, Cui Q, Dong D. LncRNADisease 2.0: an updated database of long non-coding RNA-associated diseases. Nucleic Acids Res. 2019 Jan;47 D1:D1034–7.
38. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394–424.
39. Nagaraj SH, Reverter A. A Boolean-based systems biology approach to predict novel genes associated with cancer: Application to colorectal cancer. BMC Syst Biol. 2011;5:35-. https://doi.org/10.1186/1752-0509-5-35.
40. Gao H, Song X, Kang T, Yan B, Feng L, Gao L, et al. Long noncoding RNA CRNDE functions as a competing endogenous RNA to promote metastasis and oxaliplatin resistance by sponging miR-136 in colorectal cancer. OncoTargets Ther. 2017 Jan;10:205–16.
41. Jiang H, Wang Y, Ai M, Wang H, Duan Z, Wang H, et al. 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(6):e2862-e. https://doi.org/10.1038/cddis.2017.258.
42. Ding J, Li J, Wang H, Tian Y, Xie M, He X, et al. Long noncoding RNA CRNDE promotes colorectal cancer cell proliferation via epigenetically silencing DUSP5/CDKN1A expression. Cell Death Dis. 2017;8(8):e2997-e. https://doi.org/10.1038/cddis.2017.328.
43. 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(6):2489–502.
44. Tang F, Lu Z, Wang J, Li Z, Wu W, Duan H, et al. Competitive endogenous RNA (ceRNA) regulation network of lncRNAs, miRNAs, and mRNAs in Wilms tumor. BMC Med Genomics. 2019;12(1):194-. https://doi.org/10.1186/s12920-019-0644-y.
45. Salmena L, Poliseno L, Tay Y, Kats L, Pandolfi PP. A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language? Cell. 2011 Aug;146(3):353–8.
46. Han P, Li J-W, Zhang B-M, Lv J-C, Li Y-M, Gu X-Y, et al. 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(1):9-. https://doi.org/10.1186/s12943-017-0583-1.
47. Liu C, Hou J, Shan F, Wang L, Lu H, Ren T. Long Non-Coding RNA CRNDE Promotes Colorectal Carcinoma Cell Progression and Paclitaxel Resistance by Regulating miR-126-5p/ATAD2 Axis. OncoTargets Ther. 2020 Jun;13:4931–42.
48. Wang H, Ke J, Guo Q, Barnabo Nampoukime KP, Yang P, Ma K. Long non-coding RNA CRNDE promotes the proliferation, migration and invasion of hepatocellular carcinoma cells through miR-217/MAPK1 axis. J Cell Mol Med. 2018 Dec;22(12):5862–76.
49. Chen KY, Zhu SG, He JW, Duan XP. LncRNA CRNDE is involved in radiation resistance in hepatocellular carcinoma via modulating the SP1/PDK1 axis. Neoplasma. 2022;69(4):918-30. Epub 20220602. https://doi.org/10.4149/neo_2022_211230N1853.
50. Sharma D, Subbarao G, Saxena R. Hepatoblastoma. Semin Diagn Pathol. 2017 Mar;34(2):192–200.
51. Dong R, Liu XQ, Zhang BB, Liu BH, Zheng S, Dong KR. Long non-coding RNA-CRNDE: a novel regulator of tumor growth and angiogenesis in hepatoblastoma. Oncotarget. 2017 Jun;8(26):42087–97.
52. Chen LJ, Yuan MX, Ji CY, Zhang YB, Peng YM, Zhang T,

et al. Long Non-Coding RNA CRNDE Regulates Angiogenesis in Hepatoblastoma by Targeting the MiR-203/VEGFA Axis. Pathobiology. 2020;87(3):161-70. Epub 20200317. https://doi.org/10.1159/000505131.
53. Shi J, Dong B, Cao J, Mao Y, Guan W, Peng Y, et al. Long non-coding RNA in glioma: signaling pathways. Oncotarget. 2017 Apr;8(16):27582–92.
54. Li X, Wang H. Long Non-Coding RNA GABPB1-AS1 Augments Malignancy of Glioma Cells by Sequestering MicroRNA-330 and Reinforcing the ZNF367/Cell Cycle Signaling Pathway. Neuropsychiatr Dis Treat. 2021 Jul;17:2073–87.
55. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016 Jun;131(6):803–20.
56. Li K, Xu X, He Y, Tian Y, Pan W, Xu L, et al. P21-activated kinase 7 (PAK7) interacts with and activates Wnt/β-catenin signaling pathway in breast cancer. J Cancer. 2018 Apr;9(10):1821–35.
57. Zheng J, Li XD, Wang P, Liu XB, Xue YX, Hu Y, et al. CRNDE affects the malignant biological characteristics of human glioma stem cells by negatively regulating miR-186. Oncotarget. 2015 Sep;6(28):25339–55.
58. Obexer P, Ausserlechner MJ. X-linked inhibitor of apoptosis protein - a critical death resistance regulator and therapeutic target for personalized cancer therapy. Frontiers in oncology. 2014;4:197-. https://doi.org/10.3389/fonc.2014.00197.
59. Li DX, Fei XR, Dong YF, Cheng CD, Yang Y, Deng XF, et al. The long non-coding RNA CRNDE acts as a ceRNA and promotes glioma malignancy by preventing miR-136-5p-mediated downregulation of Bcl-2 and Wnt2. Oncotarget. 2017 Oct;8(50):88163–78.
60. Zhang K, Zhang J, Han L, Pu P, Kang C. Wnt/beta-catenin signaling in glioma. J Neuroimmune Pharmacol. 2012 Dec;7(4):740–9.
61. Kapoor I, Bodo J, Hill BT, Hsi ED, Almasan A. Targeting BCL-2 in B-cell malignancies and overcoming therapeutic resistance. Cell Death Dis. 2020;11(11):941-. https://doi.org/10.1038/s41419-020-03144-y.
62. Fan YF, Yu ZP, Cui XY. lncRNA Colorectal Neoplasia Differentially Expressed (CRNDE) Promotes Proliferation and Inhibits Apoptosis in Non-Small Cell Lung Cancer Cells by Regulating the miR-641/CDK6 Axis. Med Sci Monit. 2019 Apr;25:2745–55.
63. Liu XX, Xiong HP, Huang JS, Qi K, Xu JJ. Highly expressed long non-coding RNA CRNDE promotes cell proliferation through PI3K/AKT signalling in non-small cell lung carcinoma. Clin Exp Pharmacol Physiol. 2017 Aug;44(8):895–902.
64. Zhou J, Li H, Li N, Li X, Zhang H, Song Q, et al. MicroRNA-641 inhibits lung cancer cells proliferation, metastasis but promotes apoptosis in cells by targeting PDCD4. Int J Clin Exp Pathol. 2017;10(8):8211-21. Epub 20170801.
65. Kargbo RB. Cyclin-Dependent Kinase Inhibitors in Cancer Therapeutics. ACS Med Chem Lett. 2020 Dec;12(1):11–2.
66. Zhang JJ, Fan LP. Long non-coding RNA CRNDE enhances cervical cancer progression by suppressing PUMA expression. Biomed Pharmacother. 2019 Sep;117:108726.
67. Ren L, Yang S, Cao Q, Tian J. CRNDE Contributes Cervical Cancer Progression by Regulating miR-4262/ZEB1 Axis. OncoTargets Ther. 2021 Jan;14:355–66.
68. Yu J, Zhang L. PUMA, a potent killer with or without p53. Oncogene. 2008;27 Suppl 1(Suppl 1):S71-S83. https://doi.org/10.1038/onc.2009.45.
69. Ming L, Wang P, Bank A, Yu J, Zhang L. PUMA Dissociates Bax and Bcl-X(L) to induce apoptosis in colon cancer cells. J Biol Chem. 2006 Jun;281(23):16034–42.
70. Du DX, Lian DB, Amin BH, Yan W. Long non-coding RNA CRNDE is a novel tumor promoter by modulating PI3K/AKT signal pathways in human gastric cancer. Eur Rev Med Pharmacol Sci. 2017 Dec;21(23):5392–8.
71. Hu CE, Du PZ, Zhang HD, Huang GJ. Long Noncoding RNA CRNDE Promotes Proliferation of Gastric Cancer Cells by Targeting miR-145. Cell Physiol Biochem. 2017;42(1):13–21.
72. Zhang F, Wang H, Yu J, Yao X, Yang S, Li W, et al. LncRNA CRNDE attenuates chemoresistance in gastric cancer via SRSF6-regulated alternative splicing of PICALM. Mol Cancer. 2021;20(1):6-. https://doi.org/10.1186/s12943-020-01299-y.
73. Fu D, Zang L, Li Z, Fan C, Jiang H, Men T. Long non-coding RNA CRNDE regulates the growth and migration of prostate cancer cells by targeting microRNA-146a-5p. Bioengineered. 2021 Dec;12(1):2469–79.
74. Chen JH, Tong W, Pu XF, Wang JZ. Long noncoding RNA CRNDE promotes proliferation, migration and invasion in prostate cancer through miR-101/Rap1A. Neoplasma. 2020 May;67(3):584–94.
75. Quintero-Fabián S, Arreola R, Becerril-Villanueva E, Torres-Romero JC, Arana-Argáez V, Lara-Riegos J, et al. Role of Matrix Metalloproteinases in Angiogenesis and Cancer. Frontiers in oncology. 2019;9:1370-. https://doi.org/10.3389/fonc.2019.01370.
76. Yoo D, Lee JH, Shin TH, Cheon J. Theranostic magnetic nanoparticles. Acc Chem Res. 2011 Oct;44(10):863–74.
77. Xie X, Tang B, Xiao YF, Xie R, Li BS, Dong H, et al. Long non-coding RNAs in colorectal cancer. Oncotarget. 2016 Feb;7(5):5226–39.
78. Xu MD, Qi P, Du X. Long non-coding RNAs in colorectal cancer: implications for pathogenesis and clinical application. Mod Pathol. 2014 Oct;27(10):1310–20.
79. Ren S, Wang F, Shen J, Sun Y, Xu W, Lu J, et al. Long non-coding RNA metastasis associated in lung adenocarcinoma transcript 1 derived miniRNA as a novel plasma-based biomarker for diagnosing prostate cancer. Eur J Cancer. 2013 Sep;49(13):2949–59.
80. Zhang P, Shi L, Song L, Long Y, Yuan K, Ding W, et al. LncRNA CRNDE and lncRNA SNHG7 are Promising Biomarkers for Prognosis in Synchronous Colorectal Liver Metastasis Following Hepatectomy. Cancer Manag Res. 2020 Mar;12:1681–92.
81. Xie H, Ma B, Gao Q, Zhan H, Liu Y, Chen Z, et al. Long non-coding RNA CRNDE in cancer prognosis: review and meta-analysis. Clin Chim Acta. 2018 Oct;485:262–71.
82. Liang C, Zhang B, Ge H, Xu Y, Li G, Wu J. Long non-coding RNA CRNDE as a potential prognostic biomarker in solid tumors: A meta-analysis. Clin Chim Acta. 2018

Jun;481:99–107.
83. Sun Z, Yang S, Zhou Q, Wang G, Song J, Li Z, et al. Emerging role of exosome-derived long non-coding RNAs in tumor microenvironment. Mol Cancer. 2018;17(1):82-. https://doi.org/10.1186/s12943-018-0831-z.
84. Liu T, Zhang X, Gao S, Jing F, Yang Y, Du L, et al. Exosomal long noncoding RNA CRNDE-h as a novel serum-based biomarker for diagnosis and prognosis of colorectal cancer. Oncotarget. 2016 Dec;7(51):85551–63.
85. Yu B, Du Q, Li H, Liu HY, Ye X, Zhu B, et al. Diagnostic potential of serum exosomal colorectal neoplasia differentially expressed long non-coding RNA (CRNDE-p) and microRNA-217 expression in colorectal carcinoma. Oncotarget. 2017 Jul;8(48):83745–53.
86. Fathi Dizaji B. Strategies to target long non-coding RNAs in cancer treatment: progress and challenges. Egypt J Med Hum Genet. 2020;21(1):41.