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REVIEW ARTICLE

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CRNDE: An important oncogenic long non-coding RNA in human cancers

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Abstract

Aberrant overexpression of long non-coding RNA CRNDE (Colorectal Neoplasia Differentially Expressed) is confirmed in various human cancers, which is correlated with advanced clinicopathological features and poor prognosis. CRNDE promotes cancer cell proliferation, migration and invasion, and suppresses apoptosis in complicated mechanisms, which result in the initialization and development of human cancers. In this review, we provide an overview of the oncogenic role and potential clinical applications of CRNDE.

1 | INTRODUCTION

Long non-coding RNAs (lncRNAs) are broadly defined as a class of non-coding transcripts more than 200 nucleotides in length, which lack an open reading frame.[1-3] Regardless of the fact that precise roles of the vast majority of ~40 000 lncRNAs are still under investigation,[4] lncRNAs are shown to be potential key regulators in the processes of proliferation, migration and invasion of cancer cells[5-8] by regulating gene expression patterns in various levels including the chromatin-organizational, transcriptional and post-transcriptional regulation.[9-13]

Colorectal neoplasia differentially expressed (CRNDE), first reported to be upregulated in colorectal adenomas and carcinomas, is a gene locus hCG_1815491 on chromosome 16 located on the strand opposite to the adjacent IRX5 gene.[14,15] Due to its transcripts with low coding potentials, CRNDE is classified as a long non-coding RNA.[14,15] Interestingly, CRNDE displays temporal and tissue-specific expression patterns. It is faintly expressed in normal tissues including white blood cells and colorectal mucosa, while highly expressed in breast, testis, bronchial epithelium and parotid gland.[15]

In addition, CRNDE is elevated in various cancers including colorectal cancer (CRC),[14,16-21] glioma,[22-25] hepatocellular carcinoma[26-28] and lung cancer,[29] suggesting its irreplaceable roles in the initialization and development of human cancers. Due to alternative splicing, CRNDE derives at least 10 alternative RNA transcripts, among which CRNDE-a, -b, -d, -e, -f, -h and -j are the major transcripts in cancer tissues and cell lines.[14] In general, the known splice variants of CRNDE are upregulated in both neoplastic colorectal tissues and cell lines. However, it is an exception that CRNDE-d has a decreasing trend in neoplastic colorectal tissues, which is opposed in CRC cell lines HT29, CaCo2 and HCT116.[14]

Accumulating evidence has indicated the functions of CRNDE in regulation of cancer cell proliferation, migration, invasion and apoptosis.[20,21,30-32] Furthermore, CRNDE was shown to be not only a diagnostic biomarker exhibiting high sensitivity and specificity in tissues and plasma,[14,16,33] but also a prognostic

predictor associated with clinicopathological features and outcomes in various cancers. The present review summarized current evidence regarding the abnormal expression, molecular mechanisms and clinical significance of CRNDE in human cancers (Tables 1 and 2).

2 | CRNDE IN HUMAN CANCERS

2.1 | Colorectal cancer

Many studies have demonstrated CRNDE as a remarkably upregulated lncRNA in CRC tissues and cell lines.[14,16-21] Exosomal CRNDE derived from tumour cells, which was detectable and stable, was also upregulated in the serum of CRC patients.[33,34] As an ideal prognostic predictor in colorectal cancer tissues and serum, elevated CRNDE was significantly correlated with large tumour size,[16,17] regional lymph node metastasis,[16,33,34] distant metastasis,[16,33,34] advanced pathological stage[17,20,34] and unfavourable outcomes.[16,20] Due to its potential high specificity and sensitivity for colorectal adenomas and cancer, CRNDE also served as a promising biomarker in tissues and plasma.[14,16,33]

Involved in multiple cancer-related pathways, CRNDE plays important roles in the initialization and development of CRC. Ellis et al.[35] demonstrated the mechanisms of CRNDE in the regulation of cellular metabolism in which cancer cells switch to aerobic glycolysis (Warburg effect). The repression of CRNDE by insulin and insulin-like growth factors (IGF) was eliminated by the inhibitors against either the PI3K/Akt/mTOR pathway or Raf/MAPK pathway, suggesting that CRNDE was a downstream target of both signalling cascades. Liu et al.[16,33] found that the expression of CRNDE-h was positively correlated with IRX5 in CRC tissues. Ding et al.[17] reported that the knockdown of CRNDE suppressed proliferation and induced apoptosis of CRC cells both in vitro and in vivo. Furthermore, CRNDE could epigenetically suppress the expressions of P21 and DUSP5 by recruiting EZH2, thus promoting CRC development. Jiang et al.[20] demonstrated that CRNDE could form a functional complex with hnRNPUL2 to increase its stability and direct the transport of hnRNPUL2 between the nucleus and cytoplasm, which resulted in accelerated cell proliferation and migration by activating Ras/MAPK signalling pathways.

CRNDE functions as a competing endogenous RNA to promote oncogenesis. Gao et al.[18] confirmed that CRNDE promoted metastasis and oxaliplatin resistance by sponging miR-136 and derepressing its target, E2F1. Han et al.[19] found CRNDE inhibited miR-181a-5p which targeted to beta-catenin and TCF4, and suppressed Wnt/beta-catenin signalling to promote colorectal cancer cell proliferation and chemoresistance. Yu et al.[34] revealed that CRNDE was negatively correlated with miR-217 in colorectal cancer tissues and cell lines, and served as a competing endogenous RNA (ceRNA) through binding miR-217, which results in increasing the expression of TCF7L2 to activate Wnt/beta-catenin signalling and promote cell proliferation, migration and invasion of CRC cells.[21]

2.2 | Glioma

The oncogenic role of CRNDE in glioma is another research hotspot. Zhang et al.[22] analysed the lncRNA expression patterns in a set of gene expression profiles of 268 glioma specimens, and identified 127 differentially expressed lncRNAs, among which CRNDE were found to be highly upregulated in glioma (fold change = 32.0). These are consistent with the profile results of Murat et al.,[23] Grzmil et al.[24] and Chen et al.[25] The upregulation of CRNDE was confirmed in both glioma tissues and cell lines,[30,36-38] which acted as an independent prognostic factor correlated with larger tumour size,[37] higher grade,[37] recurrence[37] and poorer overall survival.[37,39] Furthermore, the value of different transcript variants of CRNDE in clinical prognostication was also demonstrated and a low ratio of CRNDE-h/CRNDE-P predicted a more favourable disease outcomes.[39]

Multiple studies have tried to elucidate the mechanisms in which CRNDE promotes glioma. Based on bioinformatics analyses, Zhang et al.[40] predicted multiple transcription factors binding to the promoter regions of CRNDE including c-Myc, TAF1, E2F6 and SMAD, which might participate in the dysregulation of CRNDE. Wang et al.[36] reported that histone acetylation in the promoter region might account for the elevated expression of CRNDE, and CRNDE could regulate mTOR signalling by phosphorylation of P70S6K in glioma. As a miRNA sponger, CRNDE promoted the malignant biological characteristics of glioma stem cells by negatively regulating miR-186, which targets to XIAP and PAK7, and regulating their downstream proteins including MARK2, cyclin D1, BAD and caspase 3.[38] Furthermore, CRNDE also regulated the expression of miR-384 and its target PIWIL4, whose downstream proteins such as STAT3, cyclin D1, VEGFA, SLUG, MMP-9, caspase 3, Bcl-2 and Bcl-Xl, play important roles in malignant biological characteristics of glioma cells.[31] Kiang et al.[30] confirmed that the expression of CRNDE was positively correlated with EGFR activation by a microarray data analysis. Li et al.[41] found that the differentially expressed genes in CRNDE-overexpressed human astrocyte cell were involved in toll-like receptor (TLR) pathway, and further confirmed that CRNDE activated TLR3-mediated MyD88-independent TLR signalling pathway through TICAM1, PELI1 and RIPK2, and subsequently activated NF-κB and several cytokines, which finally resulted in tumourigenesis and tumour development.

2.3 | Hepatocellular carcinoma

The expression of CRNDE was significantly increased in human hepatic carcinoma (HCC) tissues and cell lines,[26,27] the former of which was consistent with the previous microarray analysis results of Jin et al.[28] who identified CRNDE as the top 20 upregulated lncRNA in 3 datasets of gene expression profiles of 117 HCC patients. Esposti et al.[42] performed RNA-Seq in 10 HCC tissues to identify and characterize differentially expressed lncRNAs, among which CRNDE was identified as one of highly upregulated lncRNA with the fold change of 1.54. Moreover, CRNDE might serve as a potential diagnostic biomarker in HCC.[26] CRNDE was important for hepatoblastoma cell

TABLE 1 Functional characterization of CRNDE in human cancers

Cancer types	Expression	Functional role	Related molecules	Related pathways	Role	References
Colorectal cancer	Upregulated	Proliferation, migration, invasion, apoptosis, chemoresistance, cellular metabolism	miR-136/E2F1, miR-181a-5p/beta-catenin/TCF4, miR-217/TCF7L2, EZH2/P21/DUSP5, hnRNPUL2, IGF, IRX5	PI3K/mTOR, Raf/Ras/MAPK, Wnt/beta-catenin signalling pathway	Oncogenic	[14,16-21,33-35]
Glioma cancer	Upregulated	Proliferation, migration, invasion, apoptosis	miR-186/XIAP/PAK7,miR-384/PIWIL4, EGFR, Bcl2/Bax,TICAM1, PELI1, RIPK2, P70S6K	mTOR, toll-like receptor (TLR), EGFR signalling pathway	Oncogenic	[22-25,30,36-40]
Hepatocellular carcinoma	Upregulated	Cell viability, proliferation, migration, invasion, angiogenesis	miR-384, NF-κB, p-AKT, p-mTOR, P70S6K	mTOR signalling pathway	Oncogenic	[26-28,42]
Lung caner	Upregulated	Proliferation and growth, apoptosis, radiosensitivity	EZH2/p21, CDK4, CDK6 and CCNE1	PI3K/AKT signalling pathway	Oncogenic	[29,43]
Ovarian cancer	Upregulated	Not determined	TP53	Not determined	Oncogenic	[44-46]
Multiple myeloma	Upregulated	Proliferation, apoptosis	miR-451	Not determined	Oncogenic	[48,49]
Breast cancer	Upregulated	Proliferation, migration, invasion	miR-136	Wnt/beta-catenin signalling pathway	Oncogenic	[32,51]
Renal cell carcinoma	Upregulated	Cell growth, proliferation	CCND1, CCNE1	Wnt/beta-catenin signalling pathway	Oncogenic	[52,53]
Gastric cancer	Upregulated	Cell viability, proliferation	miR-145/E2F3	Not determined	Oncogenic	[54]
Bladder cancer	Upregulated	Not determined	DMBT1/c-IAP1	PI3K/AKT pathway	Oncogenic	[55]

TABLE 2 Clinical significance of CRNDE in human cancers

Cancer types	Related clinical parameters	References
Colorectal cancer	Tumour size, lymph node metastasis, distant metastasis, TNM stage, unfavourable survival	[16,17,20,33,34]
Glioma cancer	Tumour size, grade, recurrence, unfavourable survival	[37,39]
Lung caner	Differentiation, lymph node metastasis, TNM stage, radiotherapy response, unfavourable survival	[29,43]
]Ovarian cancer	Recurrence, unfavourable survival	[45]
Cervical cancer	Invasion depth, lymph node metastasis, FIGO stage, unfavourable survival	[47]
Multiple myeloma	Unfavourable survival	[49]
Breast cancer	Tumour size, TNM stage, unfavourable survival	[32]
Papillary thyroid cancer	Gender, unfavourable survival	[57]

viability, proliferation and angiogenic effect in vitro as well as tumour growth and angiogenesis in vivo.[27] In mechanism, CRNDE suppressed miR-384 and regulated NF-κB and p-AKT expression to promote hepatic carcinoma cell proliferation, migration and invasion.[26] CRNDE activated mTOR signalling by regulating the phosphorylation level of mTOR and P70S6K, which resulted in promoted hepatoblastoma cell functions and angiogenic effect.[27]

2.4 | Lung caner

Zhang et al.[29] identified that CRNDE was significantly upregulated in lung adenocarcinoma (LAD) tissues and radio-resistant LAD cell lines, and was significantly correlated with poor differentiation, TNM stage and lymph node metastasis, radiotherapy response and shorter overall survival. CRNDE could interact with PRC2 and recruit its core component EZH2 to the promoter regions of p21 and repress the transcription of p21, which partly resulted in the radiosensitivity of LAD cells by affecting the G1/S transition and causing apoptosis.[29] Liu et al. found the expression of CRNDE was significantly upregulated in non-small cell lung carcinoma (NSCLC) tissues and cell lines, and promoted NSCLC cell proliferation and growth through activating PI3K/AKT signalling.[43] In addition, CRNDE modulated the expressions of CDK4, CDK6 and CCNE1, which were contributed to the cell cycle transition from G0/G1 stage to S stage.[43]

2.5 | Ovarian and cervical cancer

Fifty-four differentially expressed lncRNAs were identified in ovarian cancer-associated fibroblasts compared to normal ovarian fibroblasts, and 16 lncRNAs were differentially expressed based on survival, included MALAT1, MEG3, TUG1, XIST and CRNDE.[44] Szafron et al.[45] found that 2 elevated CRNDE transcripts (FJ466685 and FJ466686, published in GenBank 2008) negatively influenced prognosis by significantly increasing risk of death and/or recurrence on 135 ovarian carcinomas patients with platinum compounds and either cyclophosphamide (PC, n = 32) or taxanes (TP, n = 103), and the decreased expression of CRNDE was correlated with the accumulation of TP53.[46]

Han et al. found that CRNDE expression was significantly upregulated in 87 cervical cancer tissues, which was significantly correlated with the depth of cervical invasion, lymph node metastasis and FIGO stage, and predicted poorer overall survival.[47]

2.6 | Haematologic malignancies

Du et al.[48] found that 5 of 9 differentially expressed lncRNAs, GAS5, CRNDE, LOC400657, PMS2P3 and TCL0000445, were associated with inferior prognosis and corresponded with 70 genes with 30% mapped to chromosome 1 by a lncRNA analysis based on microarrays of multiple myeloma. Meng et al.[49] illustrated that CRNDE was upregulated in multiple myeloma samples and cell lines, which was closely related to tumour progression and poor survival. CRNDE induced the proliferation and antiapoptosis capability of multiple myeloma by acting as a ceRNA via negatively targeting miR-451. Subhash et al.[50] identified 5800 hypermethylated and 12 570 hypomethylated chronic lymphocytic leukaemia (CLL)-specific differentially methylated genes, among which hypermethylated CRNDE was validated and correlated with poor outcomes.

2.7 | Breast cancer

Maguire et al.[51] found that differentially spliced events expressed in SF3B1 mutant tumours including CRNDE, ICA1, OBSL1, RPL31 and TMEM14C might constitute drivers of ER-positive breast cancers. Huan et al.[32] found that CRNDE was remarkably upregulated in breast cancer tissues and cell lines, which was greatly associated with tumour size, TNM stage and unfavourable prognosis. CRNDE activated excessively Wnt/beta-catenin signalling pathway through repressing miR-136 expression.

2.8 | Other cancers

Shao et al.[52] identified CRNDE as the highly expressed gene in renal cell carcinoma (RCC) patients by published microarray analyses, which was subsequently confirmed in 15 RCC tissues and 2 cell lines. CRNDE

promoted cell proliferation through modulating the expression of CCND1 and CCNE1, and activating Wnt/beta-catenin signalling in RCC. Yang et al.[53] found that CRNDE was highly expressed in clear cell renal cell carcinoma (ccRCC) and metastatic ccRCC samples, which suggested that CRNDE was important in the progression of ccRCC. Hu et al.[54] showed that CRNDE acted as ceRNA to promote proliferation of gastric cancer cells by competitive sponging miR-145. Shen et al.[55] authenticated that CRNDE acted as a scaffold to recruit the DMBT1 and c-IAP1, resulting in promoted PI3K/AKT pathway in bladder cancer. Lili et al.[56] reported that CRNDE was upregulated in pancreatic cancer samples with a significant fold change of 1.77. A total of 734 lncRNAs were detected to be aberrantly expressed in a comprehensive study performed to screen lncRNA expression profiling with 507 papillary thyroid cancer (PTC) patients from The Cancer Genome Atlas RNA-sequencing datasets, among which CRNDE served as an ideal diagnostic factor remarkedly related to the progression and survival of PTC.[57]

3 | CONCLUDING REMARKS AND FUTURE PERSPECTIVES

As a newly characterized oncogene, CRNDE is an important lncRNA in human cancers. Accumulating evidence has confirmed the aberrant overexpression of CRNDE in various human malignancies, which is correlated with advanced clinicopathological features and poor prognosis. CRNDE promotes cancer cell proliferation, migration and invasion, and suppresses apoptosis in complicated mechanisms including competitively sponging tumour-suppressive microRNAs and recruiting chromatic modifiers. Nevertheless, the detailed regulatory mechanisms of CRNDE remain to be elucidated. In addition, efforts should be put forth to investigate the different functions of various alternative transcripts, and the lucid regulation to alternative splicing of CRNDE. In terms of clinical applications, CRNDE may serve as a potential biomarker for diagnosis and prognosis in various cancers. However, large-scale multi-centre cohort studies are expected to prove the clinical significance and practicability of CRNDE in future.

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CONFLICTS OF INTEREST

The authors declared no conflict of interests about the publication of this paper.

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