Clinica Chimica Acta 485 (2018) 262–271

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Review

Long non-coding RNA CRNDE in cancer prognosis: Review and meta-analysis

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ARTICLE INFO

Keywords:
lncRNA
CRNDE
Prognosis
Lymph node metastasis
Meta-analysis

ABSTRACT

Background: Colorectal neoplasia differentially expressed (CRNDE), a 1910-nt lncRNA encoded on human chromosome 16, has been found to be involved in various cancers. Nevertheless, the clinical and diagnostic values of CRNDE in tumors still need to be explored. In this review, we aimed to elucidate the clinical role of CRNDE in cancer by searching all correlative literature, and we sequentially explored the association between CRNDE levels and overall survival (OS) or clinicopathological characteristics of cancer.

Methods: We conducted a database search of PubMed, Wanfang Data, Ovid, SinoMed, China National Knowledge Infrastructure, Cochrane Library, and Web of Science (up to January 1, 2018). The pooled odds ratio (OR) and hazard ratio (HR) were used to assess extents of correlation between CRNDE and cancer prognosis. After identification of the inclusion and exclusion criteria, 12 articles including 1361 patients were selected for this review.

Results: The results suggested that high levels of CRNDE were highly related to poor OS in tumor patients, with pooled HRs of 2.314 (1.894–2.826, $P < .001$, fixed-effects model). Likewise, we also found that high CRNDE expression was correlated with high tumor stage [OR: 3.340, 95% confidence interval (CI): 2.417–4.616, $P < .001$, random-effects model] and lymph node metastasis (OR: 3.027, 95% CI: 2.071–4.425, $P = .004$, random-effects model).

Conclusions: Our findings demonstrated that CRNDE may modify susceptibility for various cancers and may serve as a new predictive factor for prognosis and diagnosis in different types of cancers.

1. Introduction

Because of increased medical examinations and the aging population, cancer has been identified as a severe health issue worldwide, with mortality rates that increased during most of the 20th century. In accordance with guidelines of the GLOBOCAN 2012, there were approximately 14.1 million new cancer patients and 8.2 million deaths worldwide in 2012 [1]. Likewise, cancer has been the primary cause of morbidity and mortality in China since 2010 [2]. For early-stage cancer patients without metastasis and further progression, multimodal treatments involving radical operations, neoadjuvant chemotherapy, and radiation treatments are available. However, for patients with further invasion and progression, there are still no ideal therapeutic strategies [3]. In the multi-step processes of metastasis, lymph node metastasis

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https://doi.org/10.1016/j.cca.2018.07.003
Received 28 March 2018; Received in revised form 2 July 2018; Accepted 3 July 2018
Available online 07 July 2018

(LNM) has generally been considered a key step of tumor cell dissemination [4].Therefore, the exploration of methods for early detection of cancer is critical for prognosis and treatment of cancers.

Currently, the conventional diagnostic methods for cancers include tissue biopsy, imaging, and endoscopy. These methods can cause discomfort to patients during the process or can have high false negative rates [5]. Thus, a novel, noninvasive diagnostic biomarker, which not only has high sensitivity and specificity but also is patient friendly is urgently needed. With the emerging development of next-generation sequencing (NGS) technology, studies have demonstrated that various genomic signatures are associated with LNM and high tumor stage (HTS) [6–8]. However, most studies have demonstrated molecule specificity for only a particular tumor type. A common molecular marker predicting metastasis and prognosis is needed to achieve the specificity and feasibility for effective cancer diagnosis.

Long non-coding RNAs (lncRNAs), non-coding RNA molecules longer than 200 nucleotides, play pivotal roles in various biological processes [9]. Furthermore, a growing number of studies indicate that lncRNAs are involved in different cancer types at the chromatin, transcriptional, or post-transcriptional levels [9,10]. Colorectal neoplasia differentially expressed (CRNDE), a 1910-nt lncRNA encoded on human chromosome 16 [11], has been regarded as a lncRNA, and it has a high level of expression in colorectal cancer (CRC) [12,13]. CRNDE displays tissue-specific expression in different tissues and is involved in the modification of various developmental processes [12,14]. In addition to CRC, CRNDE is also involved in breast cancer (BC) [15,16], cervical cancer (CC) [17], chronic lymphocytic leukemia (CLL) [18], hepatocellular carcinoma [19,20], ovarian cancer (OC) [21], lung adenocarcinoma (LAD), multiple myeloma (MM) [22], and glioma (GLA) [23–27]. The expression of CRNDE in these cancers is strongly correlated with patient clinical prognosis, including overall survival (OS), LNM, and HTS. CRNDE might serve as a new prognostic factor in different types of tumors. However, studies with inconsistent results have also been reported. To elucidate the relationship between CRNDE expression and tumor clinical prognosis, we performed the first meta-analysis of correlative studies to assess whether the expression of CRNDE might serve as a common molecular marker for the prognosis of various cancers.

2. Materials and methods

2.1. Literature searches

We conducted database searches in PubMed, Wanfang Data, Ovid, SinoMed, China National Knowledge Infrastructure, Cochrane Library, and Web of Science by using “CRNDE or (colorectal neoplasia differentially expressed)”and “cancer or tumor or carcinomas or neoplasm” as the keywords to identify potentially correlative reports. The search dates were up to January 1, 2018.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: [1] assessment of a relationship between high/low CRNDE expression and prognosis with cancer; [2] determination of CRNDE expression levels in tissues by quantitative real-time PCR (qRT-PCR); [3] reporting of clinicpathological parameters or outcomes, including OS, LNM, and TNM; [5] presence of sufficient data for the computation of ORs and corresponding 95% confidence interval (CI); and [6] publication in English or Chinese. The exclusion criteria were as follows: [1] animal studies, reviews, letters, abstracts, case reports, and comments; [2] studies without LNM, OS, and/or other clinicpathological parameters; and [3] studies not relevant to cancer and CRNDE.

2.3. Data extraction

Data extraction from the included literature was executed independently by two investigators (XHB and GQJ), on the basis of the inclusion and exclusion criteria. Problems were discussed and overcome by two additional authors (ZHJ and LYC). For each eligible study, the following information was collected: first author, publication date, country of origin, cancer type, total number of patients, numbers of high CRNDE expression groups and low CRNDE expression groups, numbers of patients with LNM, numbers of patients with HTS, detection method of CRNDE expression levels, follow-up month and cut-off values, multivariate analysis, hazard ratios (HRs), and corresponding 95% CI for OS.

2.4. Statistical methods

Most HRs were collected from eligible articles; the log HR and standard error (SE) were applied for integration of the survival outcome [28]. However, because some HRs might not have been directly collected from original texts, we calculated HRs with Kaplan-Meier curves by using the Engauge Digitizer version 4.1. To assess the heterogeneity among the included studies, I^2 statistics and *P* values were applied to analyze pooled HRs in this meta-analysis [29]. If the between-study heterogeneity was absent in the included studies ($I^2 < 50\%$ and P (H) > 0.1), we used fixed-effects models to analyze the results, whereas the random-effects model was applied when between-study heterogeneity was statistically necessary ($I^2 > 50\%$ or P (H) < 0.1). The underlying publication bias was evaluated by using Begg's test. To confirm the reliability of the results in this review, sensitivity analysis was conducted by using the sequential ellipsis of each individual study. All the statistical analyses were performed by using the Stata12.0. *P* values < .05 were considered statistically significant.

2.5. Quality assessment of primary studies

Two authors (XHB and GQJ) assessed the quality of the included articles. All eligible study qualities were evaluated systematically by using the Newcastle-Ottawa Scale for assessing the quality of studies in meta-analyses [30]. The detailed criteria for quality assessment are listed in Supplementary Table 1. Higher scores represent high methodological quality.

3. Results

3.1. Selection of studies

The initial search of the electronic databases returned 102 articles. After exclusion of duplicate studies, 55 potentially related articles were selected. After screening of the abstracts, uncorrelated studies were removed, and 33 latent correlated articles were included. After further identification of the full text, 21 articles without information of survival outcomes and other clinicpathological parameters were excluded. Finally, 12 articles were included for the final meta-analysis (Fig. 1).

3.2. Characteristics of eligible studies

Among these 12 articles, 1361 patients were included, with a mean patient sample size of $N = 113.42$ (range 44–251), and six studies included > 100 patients. The published period of eligible studies ranged from November 2015 to December 2017; ten studies were from China, and two studies were from Europe. Eight types of cancer were assessed in this review, with mainly digestive system malignancies. The expression of CRNDE was detected by qPCR of cancerous tissues and normalized to the expression of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), hypoxanthine-guanine phosphoribosyltransferase (HGPRT), ubiquitin C (UBC), U6, or β-actin. In the included articles,