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Review

Long noncoding RNA CYTOR in cancer: A TCGA data review

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ABSTRACT

Background and aims: Increasing evidence has shown the critical role of long non-coding RNA cytoskeleton regulator (CYTOR) in cancers. The expression of CYTOR is reported to be up-regulated in many kinds of cancers, such as gastric cancer, hepatocellular carcinoma, colon cancer, lung adenocarcinoma, oesophageal squamous cell carcinoma and renal cell carcinoma. Here, we summarized related studies and performed a meta-analysis to investigate the prognostic value of CYTOR in multiple cancers.

Methods: Eligible studies were retrieved from PubMed, Embase and Cochrane Library databases, and the role of CYTOR in cancers was evaluated by pooled odds ratios (ORs) and hazard ratios (HRs) with 95% confidence intervals (CIs). The results were further validated using The Cancer Genome Atlas (TCGA) dataset.

Results: Our results showed that elevated CYTOR expression was significantly associated with poor prognosis in cancer patients (overall survival, HR = 2.03, 95% CI = 1.73–2.38, P < 0.00001). In addition, increased CYTOR expression is associated with lymph node metastasis (OR = 2.76, 95% CI = 1.28–5.95, P = 0.01), advanced TNM stage (OR = 2.23, 95% CI = 1.48–3.38, P = 0.001) and higher tumour grade (OR = 1.54, 95% CI = 1.03–2.29, P = 0.04).

Conclusion: Overall, this study indicates that CYTOR may serve as a prognostic biomarker for cancer patients during the follow-up.

1. Introduction

Recently, many studies show that long non-coding RNAs (lncRNAs) can serve as gene expression regulators in the nucleus and cytoplasm [1–3]. These characteristics allow lncRNAs to participate in tumourigenesis and tumour progression. While a large number of lncRNAs have been sequenced and annotated, only a small proportion of them have been functionally characterized. Most of their underlying molecular mechanisms are still waiting to be confirmed. Therefore, instead of developing lncRNA-targeting therapies, discussing the potential application of lncRNAs in prognostic evaluation is more reliable, according to current evidence.

Cytoskeleton regulator (CYTOR, or long intergenic non-coding RNA 00152) is an 828-bp lncRNA that maps to chromosome 2p11.2. CYTOR was initially discovered in a study of hepatocarcinogenesis, and it has been demonstrated to regulate gene expression – by various mechanisms – as a crucial oncogene in many kinds of cancers [4–6]. In gastric cancer, for example, the overexpression of CYTOR was correlated with the functions of proliferation, apoptosis, migration, invasion, tumourigenesis and epithelial to mesenchymal transition (EMT) through binding to Enhancer of zeste homologue 2 (EZH2) and silencing the expression of p15 and p21 [5].

Clinically, CYTOR is reported to associate with poor survival and other clinical features, such as invasion depth, lymph node metastasis and TNM stage. However, the patient sample size of most studies is limited. Thus, we aim to evaluate the application of CYTOR in prognostic assessment of cancer patients. In this study, we conducted a systematic review and meta-analysis, and validated our results using the Cancer Genome Atlas (TCGA) – an independent and publicly available dataset.

Abbreviations: ceRNA, Competing endogenous RNA; COAD, Colon adenocarcinoma; DFS, Disease-free survival; EMT, Epithelial to mesenchymal transition; ESCA, Oesophageal carcinoma; HR, Hazard ratio; KICH, Kidney Chromophobe; KIRC, Kidney renal clear cell carcinoma; KIRP, Kidney renal papillary cell carcinoma; lncRNA, Long non-coding RNA; LIHC, Liver hepatocellular carcinoma; LUAD, Lung adenocarcinoma; LUSC, Lung squamous cell carcinoma; NOS, Newcastle-Ottawa Quality Assessment Scale; OS, Overall survival; qRT-PCR, Quantitative real-time reverse transcription polymerase chain reaction; RFS, Relapse-free survival; READ, Rectum adenocarcinoma; STAD, Stomach adenocarcinoma; TCGA, The Cancer Genome Atlas

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2. Materials and methods

2.1. Literature search strategies

Studies published before July 31, 2017 were systematically searched by two independent researchers (Jiayu Liang and Xin Wei) using PubMed, Embase and Cochrane Library databases without language and publication status restrictions. The following keywords were used in different combinations: long non-coding "RNA 152" or "LINCRNA00152" or "LINC00152" or "lncRNA00152" or "CYTOR" and "cancer or carcinoma or tumor or neoplasm". Additionally, potentially relevant studies that reported an association between CYTOR expression and clinical outcomes were also screened from the reference lists of the full-text articles.

2.2. Inclusion and exclusion criteria

The eligible studies were included according to the following criteria: (1) the study subjects were patients with any kind of cancer; (2) CYTOR expression levels were measured or verified by quantitative real-time reverse transcription polymerase chain reaction (qRT-PCR); (3) patients were divided into high- and low-risk subgroups based on the expression levels of CYTOR; and (4) the association between CYTOR and clinical outcome was reported. Exclusion criteria were as follows: (1) abstracts, reviews, and meta-analyses; (2) studies without patient samples; (3) studies without usable data; and (4) studies only focusing on the molecular mechanism of CYTOR. For duplicate publications, only the most recent or most informative single article was included.

2.3. Data extraction and quality assessment

The following data were extracted by two investigators independently (Jiayu Liang and Zhihong Liu): (1) publication details, specifically, first author's name, publication year and country of origin; (2) characteristics of studied subjects, such as cancer type, total cases, numbers of patients in different subgroups; (3) CYTOR assessment methods and the cut-off definition; and (4) outcome measures and hazard ratios (HR) of elevated CYTOR for OS (DFS or RFS), as well as their 95% confidence intervals (CI) and P value. Original data were requested from study authors if necessary. If only Kaplan-Meier curves were available, Engauge Digitizer version 10.1 (http://digitizer.sourceforge.net/) was used to extract data, and then, HRs and 95% CIs were calculated using the described method [7–9]. For the studies containing both univariate analysis and multivariate analysis, the HRs were obtained to analyse different subgroups. Inconsistencies in data extraction between the two independent investigators were listed and consulted by a third author (Yiping Lu). The quality of included studies was assessed independently by two other authors (Zijun Zou and Chuan Zhou) using the NOS [10], which includes three parameters: the selection parameter (maximum score is 4), the comparability parameter (maximum score is 2), and the outcome parameter (maximum score is 3). Studies with NOS score > 5 were considered to be high-quality [11].

2.4. Public data and tools

We used data from TCGA Data Portal (https://gdc-portal.nci.nih.gov/) and UCSC Xena project (http://xena.ucsc.edu), including RNAseqV2 and clinical data. This study meets the publication guidelines provided by TCGA (http://cancergenome.nih.gov/publications/publicationguidelines).

The data were analysed by GEPIA, a web server for cancer and normal gene expression profiling and interactive analyses [12]. RNA-seq datasets used by GEPIA are based on the UCSC Xena project, which are computed by a standard pipeline. One-way ANOVA was used for differential expression analysis. For the survival analysis, GEPIA used Kaplan-Meier method and log-rank test. The HR and 95% CI were also shown in the figure of Kaplan-Meier curves.

2.5. Statistical analysis

HRs with 95% CIs were used to evaluate the correlation of CYTOR expression and clinical outcomes of cancer patients. Odds ratios (ORs) with 95% CIs were estimated to identify the correlation between CYTOR expression and the clinical covariates in patients, including the TNM stage, lymph node metastasis and pathological grade. Statistical analysis was performed by utilizing RevMan 5.3 software and STATA package version 12.0 (Stata Corporation, College Station, Texas, USA). Data heterogeneity was examined by Cochran's Q test and Higgins I-squared (I^2) statistic. If the studies contained no or moderate heterogeneity ($P > 0.1$ or $I^2 < 50\%$), we used fixed-effect model; otherwise, the random-effects model was applied [13]. Publication bias was evaluated using funnel plot and Begg's and Egger's tests [14,15]. A P value < 0.05 was considered to be statistically significant.

3. Results

3.1. Characteristics of the included studies

Based on the described search criteria, 125 articles were retrieved. After excluding the duplicate articles, 84 articles were collected for the initial screening. Next, 9 records without available full-text were excluded, and a total of 31 articles were identified as original research about the functions and clinical roles of CYTOR. Full-text articles were downloaded and carefully read for eligibility. Among them, 23 studies were excluded because of non-eligible patient samples, non-eligible experimental validations, or non-eligible outcomes. Ultimately, 8 studies involving a total of 791 patients were included, and all of them came from China. Among the 8 studies, six different types of cancers were investigated, including two cases of lung adenocarcinoma (LAD) [16,17], two cases of renal cell carcinoma (RCC) [18,19], one case of gastric cancer [5], one case of oesophageal squamous cell carcinoma (ESCC) [20], one case of hepatocellular carcinoma (HCC) [21] and one case of colon cancer (CRC) [6]. The expression level of CYTOR was determined or validated in tumour samples and normal adjacent samples by qRT-PCR. The cut-off values for high- and low-CYTOR group division included median, median ratio and upper 95%CI value in control group. All 8 studies were of high quality (NOS ≥ 6). Their characteristics are listed in Table 1. The reported functional characterizations and molecular mechanisms are summarized in Table 2.

3.2. Association between CYTOR expression and overall survival (OS)

To explore the correlation between CYTOR expression and overall survival (OS), we first collected data (HR, 95%CI and P value) from 8 studies (Fig. 1). There was no statistical heterogeneity among them ($P = 0.45$, $I^2 = 0.0\%$), and the fixed-effects model was chosen. The pooled HR of high CYTOR expression group versus low CYTOR expression group was 2.03 (95%CI = 1.73–2.38, $P < 0.00001$, Fig. 2). This result suggests a close correlation between over-expressed CYTOR and poor prognosis. More importantly, when additional multivariate analysis from three studies are merged [5,6,18], the expression level of CYTOR showed an independent ability to predict the prognostic risk for patients (HR = 2.18, 95% CI = 1.51–3.15, $P < 0.0001$, Fig. 3).

Next, we divided the 8 studies into several subgroups based on the cancers from different systems (respiratory system, urinary system and digestive system). This analysis shows that CYTOR could be a prognostic indicator of OS in cancers from respiratory system (HR = 1.72, 95% CI = 1.29–2.29, $P = 0.0002$, $I^2 = 0\%$), urinary system (HR = 2.28, 95% CI = 1.71–3.03, $P < 0.00001$, $I^2 = 44\%$) and digestive system (HR = 2.11, 95% CI = 1.63–2.74, $P < 0.00001$, $I^2 = 0\%$) (Table 3 and Fig. 4). We conducted another subgroup meta-analysis based on an expression cut-off (high/low). The results reveal