Clinica Chimica Acta 468 (2017) 10–16

Contents lists available at ScienceDirect

Clinica Chimica Acta

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

Long noncoding RNA activated by TGF-β in human cancers: A meta-analysis

Yang-Hua Fan [1], Chen-xing Ji [1], Bing Xu, Heng-yi Fan, Zu-jue Cheng *, Xin-Gen Zhu *

Department of Neurosurgery, The Second Affiliated Hospital, Nanchang University, Nanchang, China

ARTICLE INFO

Article history:
Received 4 December 2016
Received in revised form 30 January 2017
Accepted 1 February 2017
Available online 3 February 2017

Keywords:
LncRNA-ATB
Neoplasm
Metastasis
Prognosis
Meta-analysis

ABSTRACT

Background: Because long non-coding RNA ATB (activated by TGF-β) is dysregulated in many cancers, we performed a meta-analysis to determine its prognostic potential in malignant tumors.
Methods: We searched electronic databases, including PubMed, Medline, OVID, Cochrane Library and Web of Science from inception until November 15, 2016 and identified eight studies with 818 cancer patients for the meta-analysis. We analyzed the hazard ratios (HRs) and 95% confidence intervals (CIs) to determine the relationship between lncRNA-ATB expression and overall survival (OS), recurrence -free survival (RFS), disease-free survival (DFS). We also use RevMan5.3 software to calculate odds ratio (ORs) to assess the association between lncRNA-ATB expression and pathological parameters including lymph node metastasis (LNM), distant metastasis (DM) and tumor stage.
Results: Our analysis showed that increased lncRNA-ATB expression was associated with OS (HR = 2.82, 95% CI:1.98–4.00, $P < 0.00001$), DFS (HR = 2.75, 95% CI:1.73–4.38, $P < 0.0001$), RFS(HR = 3.96, 95% CI:2.30–6.81, $P < 0.00001$), LNM (OR = 4.07, 95% CI 1.74–9.53, $P = 0.001$), DM (OR = 3.21, 95% CI 1.06–9.72, $P = 0.04$) and high tumor stage (OR = 2.81, 95% 1.78–4.43, $P < 0.0001$) in patients with other types of cancers that excluded pancreatic cancer.
Conclusions: Meta-analysis demonstrated that increased lncRNA-ATB expression can be a useful prognostic biomarker in human cancer.

Contents

Abbreviations: ATB, activated by TGF-β; HR, hazard ratio; CI, confidence interval; OR, odds ratio; CRC, colorectal cancer; NSCLC, non-small cell lung cancer; PRC, pancreatic cancer; GC, gastric cancer; RCC, renal cell carcinoma; PSC, prostate carcinoma; HCC, hepatocellular carcinoma; LNM, lymph node metastasis; DM, distant metastasis; HTS, high tumor stage; OS, overall survival; DFS, disease-free survival; RFS, recurrence -free survival; NOS, Newcastle-Ottawa Scale.

* Corresponding authors at: Department of Neurosurgery, The Second Affiliated Hospital, Nanchang University, 1 Minde Road, Nanchang 330006, Jiangxi, People's Republic of China.
E-mail addresses: chengzjsjwk2016@163.com (Z. Cheng), xingenzhu_2015@sina.com (X.-G. Zhu).

[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.cca.2017.02.001
0009-8981/

1. Introduction

In 2012, 8.2 and 14.1 million people died from and were diagnosed with cancer worldwide, respectively [1]. The American National Center for Health Statistics estimated that nearly 600,000 Americans will die from cancer in 2016 [2]. The five year survival rate of most cancers is extremely low and since survival depends on early diagnosis of cancer, there is a constant need to identify and develop better diagnostic and prognostic markers.

Long noncoding RNA (lncRNA) are transcribed RNA molecules are >200 nucleotides in length that lack an open reading frame [3]. They are involved in epigenetic regulation, transcriptional and posttranscriptional regulation, ie, key cellular processes that determine tumorigenesis [4]. Dysregulation of lncRNAs has been reported in many types of cancers [5–8]. Because they have been implicated in different stages of cancer progression including proliferation, invasion and metastasis, they appear to be promising prognostic markers [9–11].

LncRNA-ATB (activated by TGF-β) was first reported as highly expressed in hepatocellular carcinoma and showed extensive regulatory functions. This lncRNA, located on chromosome 14, induces epithelial-mesenchymal transition (EMT) and promotes hepatocellular carcinoma cell invasion through the TGF-b/miR-200 s/ZEB signaling pathway [12–13]. Because lncRNA-ATB expression is involved in cancer growth and metastasis, it is a promising prognostic biomarker candidate for human cancer [14].

Unfortunately, most studies regarding lncRNA-ATB are limited by discrete outcomes and small patient sample. Therefore, we performed this meta-analysis to determine the prognostic value of lncRNA-ATB by combined analysis of data from multiple studies.

2. Methods

2.1. Literature search to identify relevant studies for meta-analysis

A systematic search of multiple electronic databases, Medline, Pubmed, OVID, and Web of Science, was performed independently by two authors, Yanghua Fan and Hua Fang in accordance with the standard guidelines of meta-analysis. Literature was searched from inception until November 15, 2016 for articles that reported lncRNA-ATB as a probable prognostic marker for survival of cancer patients [15–16]. Searches were performed by both the text word and MeSH strategy and included terms like 'lncRNA-ATB', 'long noncoding RNA activated by TGF-β', 'ATB or activated by TGF-β', 'lncRNA', 'noncoding RNA', 'long intergenic noncoding RNA', 'carcinoma', 'neoplasm', 'tumor', 'cancer', 'prognostic', 'prognosis', 'outcome', 'survival' or 'recurrence'. The strategy was adjusted in different databases to maximize search findings. Manual searches were also performed using the reference lists of the relevant articles to retrieve eligible studies for inclusion.

2.2. Selection criteria for including studies in meta-analysis

The two researchers, Yanghua Fan and Chen-xing Ji, independently evaluated all data to select relevant studies for meta-analysis. The criteria used to include studies in the meta-analysis were: 1) the relationship between lncRNA-ATB expression and survival was measured in multiple human tumors; 2) the expression level of lncRNA-ATB was measured either in human tumor tissue and the patients were grouped according to lncRNA-ATB expression; and 3) all tumors were confirmed by pathologic or histologic exam with pathologic parameters such as LNM and tumor stage described.

The criteria to exclude studies were: 1) articles that were reviews, letters, editorials, case reports and expert opinions; 2) non-English language and non-human studies; 3) studies lacking data listed in the criteria for included studies; and 4) basic characterization studies of lncRNA-ATB.

2.3. Data extraction from relevant studies for meta-analysis

The two reviewers, Yanghua Fan and Zu-jue Cheng, independently extracted and examined the data from the selected original articles. Disagreements in assessment were resolved through consensus with a third reviewer, Xingen Zhu. The following details were collected from each of the study: surname of the first author, publication year, country, tumor type, sample size, the number of patients with lymph node metastasis and high tumor stage, HR and 95% CI of elevated lncRNA-ATB for survival(OS, DFS, RFS), the Newcastle-Ottawa Scale (NOS) score and the detection method of lncRNA-ATB.

The study quality was assessed in accordance with the Newcastle-Ottawa Scale (NOS). A total of nine items, each of which was assigned a score of 1, were measured in each study. The total scores for different studies ranged from 0 to 9. If the score was ≥ 7, the study was considered to be of high quality.

2.4. Statistical analysis

The statistical analysis was performed by RevMan version 5.3 software. The heterogeneity among different studies was measured by the Q and I^2 tests. A probability value of $I^2 \geq 50\%$ and $P < 0.1$ indicated the existence of significant heterogeneity [17]. A random effects model or fixed effects model was selected based on the results of heterogeneity analysis. The random-effects model was used if there was significant heterogeneity among the studies or else, the fixed effects model was used. The potential publication bias was assessed by the Begg's funnel plot through Stata 12.0 software. Pooled HRs and ORs were obtained from the published data. We used the HRs and 95% CIs reported in a publication when it was available and when they were not reported, the HR values were estimated from the survival information obtained from Kaplan-Meier curve. OS, DFS, RFS were calculated using the log HR and standard error (SE) values [18]. Odds ratios (ORs) and their 95% CIs were used to assess the association between lncRNA-ATB expression and the tumor parameters, including LNM, DM and tumor stage.

3. Results

3.1. Literature search analysis results

The detailed screening process of lncRNA-ATB studies is shown in Fig. 1. A total of 34 records were retrieved from the databases in initial search and 19 duplicate reports were excluded. After detailed screening of the title and abstract, seven irrelevant and non-comparative articles [13,26–31] were excluded. After reviewing the full text of the remaining 9 studies, the article [14] by Ma et al. was excluded because of insufficient data to estimate HR for further analysis. Based on the inclusion and exclusion criteria, a total of eight studies and 818 patients were included in the meta-analysis [12,19–25].