Long non-coding RNA HOTTIP is able to predict poor prognosis in various neoplasms: A meta-analysis

NING JIN1*, LING-YUN YANG2* and ZI-PENG XU3

1Department of Pathology, The Second Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210011; 2Department of Pediatrics, Wuxi Children's Hospital, Wuxi, Jiangsu 214002; 3Department of General Surgery, Xishan People's Hospital, Wuxi, Jiangsu 214011, P.R. China

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Abstract. HOXA distal transcript antisense RNA (HOTTIP), a critical oncogenic long non-coding RNA, has been reported to be aberrantly regulated in various cancer types. The present meta-analysis aimed to investigate HOTTIP as a potential clinical applicable prognostic biomarker in malignant neoplasms. Literature collections were performed by searching the electronic databases, PubMed and Web of Science (up to July 20, 2016). All the relevant searches were conducted to identify the association of HOTTIP with the overall survival (OS) rate. A total of six articles consisting of 508 patients were included in the present meta-analysis. The results suggested that the overexpression of HOTTIP is closely correlated with poor OS (hazard ratio=2.28; 95% confidence interval=1.71-3.04; P=0.000). In conclusion, the present meta-analysis has demonstrated that an increased expression level of HOTTIP is correlated with poor OS in different types of cancer, suggesting that HOTTIP potentially serves as a reliable prognostic biomarker in different types of cancer.

Introduction

Long non-coding RNAs (lncRNAs) are a class of transcripts >200 nucleotides in length with limited protein-coding potential (1). Recently, several studies have revealed that lncRNAs are dysregulated in numerous types of human cancers, including gastric, colorectal, gastric, ovarian, lung and breast cancer (2-7). Certain lncRNAs have multiple functions in a wide range of biological processes, including proliferation, apoptosis, or cell migration (2,3,6).

Correspondence to: Dr Zi-Peng Xu, Department of General Surgery, Xishan People’s Hospital, 588 Guangrui Road, Wuxi, Jiangsu 214011, P.R. China
E-mail: xuzipeng1989@126.com

*Contributed equally

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evaluate the heterogeneity of the data (16). The random-effects model was used if there was significant heterogeneity between studies ($I^2 > 50\%$ or $P < 0.05$), whereas the fixed-effects model was applied for the present meta-analysis. The meta-analysis results were displayed using Forest plots. The stability of the results was evaluated using sensitivity analysis. Begg's funnel plots were used to evaluate publication bias (17). All the statistical analyses were performed using Stata 12.0 (Stata Corporation, College Station, TX, USA).

Results

As shown in Fig. 1, the searches with key terms disclosed that 64 articles that had been published up to July 20, 2016. After screening the title and abstract carefully, 56 references were excluded due to duplicate publications and irrelevant content. Upon further review of the full articles, 2 were excluded since they were records lacking information concerning the survival outcomes. Finally, 6 articles consisting of 508 patients were included in the present meta-analysis. Among these 6 studies, 5 came from China and 1 was from Switzerland. Five different types of cancer were evaluated, with 2 cases of hepatocellular carcinoma, 1 case of tongue squamous cell carcinoma, 1 case of colorectal cancer, 1 of osteosarcoma, and 1 of gastric cancer. All these characteristics are summarized in Table I.

Association between HOTTIP and OS. To investigate the association between HOTTIP expression and OS, 6 studies consisting of 508 patients were included. Heterogeneity analysis revealed that no evidence of statistically significant heterogeneity across these 6 studies was identified ($P=0.983$ for heterogeneity test; $I^2=0\%$). Subsequently, a fixed-effect model was used to calculate the HR with corresponding 95% CI. According to the meta-analysis results (HR=2.28; 95% CI=1.71-3.04; $P<0.0001$, Fig. 2), it may be concluded that patients for whom a high expression of HOTTIP in cancerous tissues was detected were more prone to a poor outcome.

Sensitivity analysis and publication bias. Sensitivity analysis indicated that the exclusion of any individual study did not change the significance of HR (Fig. 3). This demonstrated that the HR of the OS was reliable. A Begg's funnel plot and Egger's linear regression test were performed to evaluate publication bias. The Egger's and Begg's tests suggested the publication bias was not significant ($P=0.151$ for Egger's test; $P=0.06$ for Begg's test) (Fig. 4).

Discussion

HOTTIP is an lncRNA transcribed from the 5'-end of the HOXA. It is able to bind to and target WD repeat-containing
protein 5 (WDR5)/mixed lineage leukemia (MLL) complexes to the 5'-HOXA locus, driving histone H3 lysine 4 trimethylation and gene transcription (8). The most recently published studies have identified that HOTTIP is a critical oncogenic lncRNA that is highly expressed in numerous types of cancers, including hepatocellular carcinoma and colorectal, gastric, and lung cancer. At the same time, these studies have demonstrated that the HOTTIP/HOXA13 axis is associated with cell growth and the cell cycle, which serves an important role in the genesis and progression of cancer (18,19). Although it has already been demonstrated that HOTTIP is closely associated with multiple tumors, the prognostic role of HOTTIP expression in different types of cancer has yet to be fully elucidated. Therefore, a meta-analysis was performed to explore the connection between a high expression level of HOTTIP and the OS rate for cancer patients. The present meta-analysis has highlighted the tumor prognostic role of HOTTIP, and provided sufficient evidence to establish an association between HOTTIP expression and the prognosis of different human cancer types, suggesting that over-expression of HOTTIP is significantly corrected with poor OS. However, it should be emphasized that there were several limitations in the present study. First, the cut-off definition of HOTTIP expression varied in each study. Secondly, only 6 studies with 508 patients were included in the present meta-analysis, which may influence the reliability of our results. Thirdly, three HRs in our study were calculated according to the survival curve, which may have affected the accuracy of the research results. Fourthly, only English language papers were included in the present study.

Taken together, the present meta-analysis has demonstrated that elevated levels of HOTTIP expression are significantly associated with a poor OS (HR=2.28; 95% CI=1.71-3.04; P<0.0001). Therefore, HOTTIP may be used as a negative, unfavorable prognostic marker for most types of cancer.

References