

Clinical value of lncRNA ZFAS1 in various cancers: an updated meta-analysis of 2263 cancer patients

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Abstract

Background: LncRNA ZNF1 antisense RNA 1 (ZFAS1) is largely reported to be abnormally expressed in various human cancers and associated with unfavorable prognosis. So this study aims to further investigate its clinical value in multifarious cancers.

Methods: Databases of PubMed, Web of science, Cochrane library, Embase, Chinese National Knowledge Infrastructure and Wanfang was retrieved to collect eligible studies until October 22, 2020. The clinical role of ZFAS1 was comprehensively assessed by STATA 12.0. Additionally, the CeRNA network in which ZFAS1 involved was constructed. And function analysis of targeted mRNAs was performed by R package "cluster profiler".

Results: 23 studies of 2263 cancer patients met the inclusion criteria in this meta-analysis. The comprehensive results suggested that patients with elevated ZFAS1 expression got poor overall survival (OS) (HR=1.80, 95%CI: 1.50-2.10, $P\leq 0.001$), and they are prone to lymph node metastasis (OR=2.67, 95%CI: 1.73-4.14, $P\leq 0.001$), distant metastasis (DM) (OR=3.45, 95%CI: 1.61-7.39, $P=0.001$), advanced TNM stage (HTS) (OR=2.99, 95%CI: 1.97-4.54, $P\leq 0.001$), larger tumor size (LTS) (OR=1.54, 95%CI: 1.05-2.24, $P\leq 0.001$), poor histologic grade (PHG) (OR=1.57, 95%CI: 1.09-2.26, $P=0.015$). The CeRNA network and function analysis revealed the potential mechanism which ZFAS1 may involve in cancers.

Conclusion: The current analysis revealed that elevated ZFAS1 expression is common in various cancer and was significantly associated with poor OS and clinical characteristics, thus it may function as prognostic biomarker in various cancer. Nevertheless, larger well-designed clinical research is still warranted to verify our findings.

Background

Cancer, as one of the leading causes of death, with high morbidity, has continually imposed heavy economical burdens on society and families. According to the latest report, 1,806,590 new cancer cases and 606,520 cancer-related deaths will occur in the United States in 2020 [1]. This severe situation has made numerous researchers to concentrate on the study of early diagnosis and efficient treatment of cancer patients. Indeed, the death rate has gradually decline with great advancement made in diagnosis and therapy of cancer, but the 5-year survival rate of cancer patients is still disappointing [2]. Thus, it's of great need to seek useful therapeutic and prognostic biomarker for the improvement of cancer patients' prognosis.

Long non-coding RNA (lncRNA), with length of more than 200 nucleotides, is a classic kind of non-coding RNA which lacks of protein coding ability. Existing evidence have proved that lncRNA can act as a significant gene regulator and participate in various biological process, including epigenetic regulation, cell cycle, alternative splicing, chromatin modification and so on [3-5]. Importantly, it's also confirmed that lncRNA can function as oncogene or tumor-suppressing gene through control of tumorigenesis, invasion, progression and metastasis in multiple cancers [6-8].

LncRNA ZNF1 antisense RNA 1 (ZFAS1, also known as Zinc finger antisense 1), which transcribed from the antisense orientation of zinc finger NFX1-type containing 1(ZNF1), is located on chromosome 20q13.13 [9]. Growing studies have reported abnormal expression of ZFAS1 in diverse cancers, including pancreatic cancer [10], hepatocellular carcinoma [11], melanoma [12], esophageal squamous cell carcinoma [13] and so on. Moreover, elevated ZFAS1 expression is reported to be related to poor prognosis and clinical characteristics in various cancers [14-16], which indicate that ZFAS1 may serve as a promising biomarker for the prognosis and therapy of cancer patients. However, limited by insufficient sample size in single study and inconsistent findings among studies, the clinical role of ZFAS1 in cancer deserve further study to confirm. So we performed this updated meta-analysis to comprehensively evaluate the association between ZFAS1 expression and OS and clinicopathological characteristics of cancer patients.

Methods

Study selection

The reporting of this meta-analysis complied with the Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17]. Selection of eligible studies was performed in databases of PubMed, Web of Science, Chinese National Knowledge Infrastructure and Wanfang up to October 2020. The search terms were: ("lncRNA ZFAS1" or "lncRNA ZNF1 antisense RNA 1") AND ("cancer" or "carcinoma" or "tumor" or "malignancy").

Inclusion and exclusion criteria

Inclusion criteria were as follows: (a) the ZFAS1 expression of human tumor tissues were detected via method of qRT-PCR; (b) cancer patients were divided into high expression group and low expression group according to median or average expression level of ZFAS1; (c) study provided survival information and clinicopathological parameters of cancer patients according to different ZFAS1 expression.

Studies will be excluded if they meet one or more criteria as following: (a) reviews, case reports, letters, meta-analysis, conference articles and laboratory study; (b) study without survival information or clinicopathological features of patients; (c) high or low ZFAS1 expression were not defined.

Data extraction and quality assessment

In strict accordance with inclusion and exclusion criteria, qualified original literature data assessment and related data extraction were independently completed by two investigators (Zhou Liu and Biyun Lu), and any disagreement encountered is resolved through consultation with third investigator (Kaiyuan Chen). The following information was extracted from each literature: first author, publication year, country, tumor type, detection method, total number of cases, survival information and clinicopathological parameters. If there were both univariate and multivariate analysis in the include study, the results of multivariate analysis will be applied. If only the survival curve is provided in the study, then Engauge Digitizer v10.4 software will be employed to extract HR and 95% CI. Quality assessment was conducted through Newcastle-Ottawa-Scale (NOS) criteria. High-quality studies were defined as the NOS score ≥ 6 .

CeRNA network construction

By using starbase v2.0 (<http://starbase.sysu.edu.cn/>), the targeted miRNA of ZFAS1 was predicted. And the targeted mRNA mining of predicted miRNA was performed via miRWalk with the filter set as 0.95, 3UTR, TargetScan, miRDB, miRTarBase. Then the targeted mRNAs were applied to perform Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis by R package "cluster profiler".

Statistical analysis

Stata 12.0 software (StataCorp, College Station, Texas USA) was used to analyze the extracted data. Pooled hazards ratios (HRs) or odds ratios (ORs) with 95% confidence interval (CI) were used to assess the correlation of prognosis and clinicopathological features with ZFAS1 expression, respectively. Heterogeneity test was performed by Cochran's Q test and I^2 statistic. Random-effect model was used if the heterogeneity was significant ($I^2 \geq 50\%$, and $P < 0.05$), instead, fixed-effect model will be chosen. The robustness and heterogeneity source of results was tested via sensitivity analysis and subgroup analysis, respectively. Potential publication bias was assessed by and Begg's test and $P > |z| \geq 0.05$ indicates no publication bias existed. Statistically significance was defined if $P < 0.05$.

Results

Details of included study

As shown in Figure 1, after strict selection by two authors, 23 studies of 2263 cancer patients were included in this study. The detailed characteristics of the 23 studies were summarized in Table1. Those studies were published from 2015 to 2020, with average sample size about 103. The included 2263 patients all come from China. 16 types of tumors were included in this study, which contains pancreatic adenocarcinoma (PAAD) [10], hepatocellular carcinoma (HCC) [11, 18], melanoma [12], esophageal squamous cell carcinoma (ESCC) [13, 19], hepatoblastoma (HB) [20], cholangiocarcinoma (CCA) [14], papillary thyroid carcinoma (PTC) [21], prostate cancer (PCa) [22], clear cell renal cell carcinoma (ccRCC) [15], colorectal cancer (CRC) [16, 23, 24], bladder cancer [25, 26], nasopharyngeal carcinoma (NPC) [27], gastric cancer (GC) [28], epithelial ovarian cancer (EOC) [29], non-small cell lung cancer (NSCLC) [30], glioma [31]. ZFAS1 expression in tumor tissues were all detected by qRT-PCR. The NOS score of included studies are all ≥ 6 which means they are all high quality studies. Additionally, the study of Shi et al. provided two independent cohorts of patients, so we didn't merge the data together, but named the data from primary cohort as Shi HT and the validation cohort as Shi HT-1.

ZFAS1 expression and OS

In this part, 16 studies of 1637 patients were included. Among them, 5 studies directly provided HR and 95%CI, and the survival data from the other 11 studies were indirectly extracted from survive curve. The results revealed that patients with high ZFAS1 expression underwent poor OS (OR=1.80, 95%CI: 1.50-2.10, $P \leq 0.001$, Figure 2). It's found that many different characteristics were existed among the study of OS, therefore, to exclude potential bias, subgroup analysis on the basis of HR methods, sample size, follow-up month and tumor type indicate that high ZFAS1 expression was correlated to poor OS in the above 8 subgroups (Figure 3), which indicates there exists no potential bias in study about OS. Additionally, sensitivity analysis and Begg's test further confirms the robustness of this results (Figure 4).

ZFAS1 expression and clinical characteristics

OR and 95%CI was applied to evaluate the relationship between ZFAS1 expression and various clinical characteristics. As manifested in Figure 5, the results demonstrated that high ZFAS1 expression was related to high tumor stage (HTS) (OR=2.99, 95%CI: 1.97-4.54, $P \leq 0.001$, Figure 5a), larger tumor size (LTS) (OR=1.54, 95%CI: 1.05-2.24, $P \leq 0.001$, Figure 5b), lymph node metastasis (LNM) (OR=2.67, 95%CI: 1.73-4.14, $P \leq 0.001$, Figure 5c), poor histologic grade (PHG) (OR=1.57, 95%CI: 1.09-2.26, $P = 0.015$, Figure 5d), distant metastasis (DM) (OR=3.45, 95%CI: 1.61-7.39, $P = 0.001$, Figure S1a), but not to age (OR=1.06, 95%CI: 0.89-1.26, $P = 0.499$, Figure S1b) and gender (OR=1.13, 95%CI: 0.94-1.36, $P = 0.209$, Figure S1c).

And Begg's test in Figure 6 manifested that there exists no publication bias in the studies of LNM ($Pr > |z| = 0.322$), DM ($Pr > |z| = 0.060$), HTS ($Pr > |z| = 0.173$), LTS ($Pr > |z| = 1.000$), PHG ($Pr > |z| = 0.381$).

CeRNA network

Growing studies have found out that CeRNA network plays a significant role in the regulation of lncRNA to cancer. To explore the potential mechanism of ZFAS1 in cancer development, the CeRNA network centered on ZFAS1 was constructed. As shown in Figure 6, this CeRNA network which contains 95 nodes and 103 edges manifested lots of ZFAS1/miRNA/mRNA axis that may participate in the regulation of occurrence and development of cancer. GO and KEGG analysis indicated the biological functions and pathway the targeted mRNAs may involve in. Those results above together provide meaningful clues for future mechanism research of ZFAS1 in cancer.

Discussion

Cancer has always been a great concern to human health. Due to its undetectable onset, when diagnosed, most cancer patients tend to have advanced clinical stage, LNM and DM, and current cancer therapy can't effectively stop its development, which make them unfortunately miss the optimal treatment time and have poor prognosis. Therefore, the identification of prospective biomarker for the diagnosis, treatment and prognosis of cancer is urgent.

Recently, plenty of studies indicated that several lncRNAs may serve as a promising prognostic biomarker for cancer patients, such as SNHG1 [32], linc00152 [33], PCAT-1 [34], FAM83H-AS1 [35] and so on. And ZFAS1 is exactly one of them. In this meta-analysis, our results showed that increased ZFAS1 expression can predict poor prognosis in diverse cancer patients (OR=1.80, 95%CI: 1.50-2.10, $P \leq 0.001$). Furthermore, subgroup analysis, sensitivity analysis and Begg's test performed in this study showed that no potential heterogeneity exists among included studies, which further testified the stability of our results. Meanwhile, elevated ZFAS1 expression was also associated with clinical characteristics, including HTS (OR=2.99, 95%CI: 1.97-4.54, $P \leq 0.001$), larger tumor size (OR=1.54, 95%CI: 1.05-2.24, $P \leq 0.001$), LNM (OR=2.67, 95%CI: 1.73-4.14, $P \leq 0.001$), PHG (OR=1.57, 95%CI: 1.09-2.26, $P = 0.015$), DM (OR=3.45, 95%CI: 1.61-7.39, $P = 0.001$). Taken together, our results demonstrated that upregulated ZFAS1 expression can be regarded as specific indicator of poor prognosis in cancer patients.

Since ZFAS1 was firstly discovered by Askarian-Amiri in breast cancer [9], mounting evidence have demonstrated that the dysregulation of ZFAS1 expression plays a critical role in the proliferation, invasion and metastasis of various cancers. And the carcinogenic molecular mechanism of ZFAS1 has been partly clarified that it usually functions as CeRNA of miRNA to regulate downstream mRNA expression to affect manifold biological behaviors of tumor cell. Duan et al. found that ZFAS1 was obviously overexpressed in HCC and connected with worse prognosis of HCC patients, and silencing of ZFAS1 can suppress cell proliferation, invasion, migration and epithelial-mesenchymal transition (EMT) through regulation of the miR-624/MDK/ERK/JNK/AKT signaling pathway [11]. Several researchers have demonstrated that ZFAS1 was upregulated in CRC and can serve as a prognostic factor for CRC patients. Among them, Chen et al. revealed that ZFAS1 can promote tumor growth, metastasis, and angiogenesis in CRC thorough sponging of miR-150-5p [16]; Xie et al. found that ZFAS1 promotes cell proliferation and invasion in CRC via sponging to miR-484 [23]; and Fang et al. demonstrated that ZFAS1 facilitates the progression of CRC by regulation of ZEB1 expression [36]. Meanwhile, ZFAS1 can exert oncogenic effect in PAAD through miR-3924/ROCK2 pathway [10], and knockdown of ZFAS1 can reduce tumor progression in ovarian cancer via sponging of miR-150-5p to modulate RAB9A expression [29]. Xiao et al. noted that ZFAS1 acts as CeRNA of miR-193a-3p to control HB growth by targeting RALY via HGF/c-Met Pathway. Moreover, the CeRNA network build in our study may lead to another novel direction on the path of cancer mechanism research about ZFAS1.

Notably, several researchers have explored the role of ZFAS1 in cancers before our meta-analysis, but obvious difference can be observed in our study. Firstly, a total of 23 studies of 2263 cancer patients were included in our study, the most sample size in studies of Dong et al. [37] is only 12 studies of 1075 patients, therefore, larger sample size in our study make our findings more convincing. Secondly, the prognostic role of ZFAS1 in more cancer types including PAAD, ESCC, HB, CCA, PTC, PCa, ccRCC, NPC and bladder cancer were explored in current study, which make our results more applicable. Thirdly, we firstly revealed that high ZFAS1 expression is significantly with DM. Lastly, we firstly constructed a CeRNA network in which ZFAS1 participated, which contribute to the discovery of new regulation mechanism.

However, it's undeniable that some limitations can be found in our study. Firstly, patients included in our study are all Chinese, which may restrict the applicability of our findings in other race. Secondly, some HRs were extracted from survive curve, which may affect the reliability of our results. Lastly, the cut-off value defines high and low expression of ZFAS1 were not consistent among studies, which may cause potential heterogeneity. Consequently, more studies of high-quality and diverse ethnicity are required to further verify our findings.

Conclusions

In short, our findings indicated that high ZFAS1 expression is significantly associated with poor OS and clinicopathological features including advanced tumor stage, lymph node metastasis, larger tumor size, poor differentiation and distant metastasis in cancer patients, thus it may be qualified as a prognostic biomarker for cancer patients.

Abbreviations

ZFAS1: ZNFX1 antisense RNA 1; OS: overall survival; lncRNA: Long non-coding RNA; ZNFX1: zinc finger NFX1-type containing 1; NOS: Newcastle-Ottawa-Scale; GO: Gene Ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes; HR: hazards ratios; OR: odds ratios; CI: confidence interval; PAAD: pancreatic adenocarcinoma; HCC: hepatocellular carcinoma; ESCC: esophageal squamous cell carcinoma; HB: hepatoblastoma; CCA: cholangiocarcinoma; PTC: papillary thyroid carcinoma; PCa: prostate cancer; ccRCC: clear cell renal cell carcinoma; CRC: colorectal cancer; NPC: nasopharyngeal carcinoma; GC: gastric cancer; EOC: epithelial ovarian cancer; NSCLC: non-small cell lung cancer; HTS: high tumor stage; LTS: larger tumor size; LNM: lymph node metastasis; PHG: poor histologic grade; DM: distant metastasis.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All the listed authors agree to publish.

Availability of data and materials

All data are included in this article.

Competing interests

The authors declare no underlying conflicts of interest.

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Authors' contributions

Conception: ZL, GL. Data analysis: BL, KC. Manuscript draft: ZL, BL, WG. Manuscript revision: GL, SP. All authors read and approved the final manuscript.

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Tables

Table 1 Main characteristics of included studies. Note: indirectly, HR extracted from survival curve; directly, HR extracted from paper; -, not available; OS, overall survival.

study	year	country	tumor type	sample size(n)	ZFAS1 expression		outcome information	Hazard Ratios methods	follow-up months	Laboratory method	NOS score
					high	low					
Liu JY	2020	China	pancreatic adenocarcinoma	83	20	63	OS	indirectly	>60	qRT-PCR	7
Duan R	2020	China	hepatocellular carcinoma	94	47	47	OS	indirectly	≤60	qRT-PCR	8
Liang LL	2019	China	melanoma	45	23	22	OS	indirectly	≤60	qRT-PCR	6
Li ZR	2019	China	esophageal squamous cell carcinoma	136	69	67	-	-	-	qRT-PCR	7
Cui XC	2019	China	hepatoblastoma	70	42	28	-	-	-	qRT-PCR	8
Li ZL	2019	China	cholangiocarcinoma	64	30	34	OS	indirectly	≤60	qRT-PCR	7
Tong HC	2019	China	papillary thyroid carcinoma	80	48	32	-	-	-	qRT-PCR	8
Cui XL	2019	China	prostate cancer	52	26	26	-	-	-	qRT-PCR	8
Dong D	2019	China	clear cell renal cell carcinoma	60	30	30	OS	indirectly	≤60	qRT-PCR	6
Chen XX	2018	China	colorectal cancer	112	56	56	OS	directly	>60	qRT-PCR	8
Chen X	2018	China	nasopharyngeal carcinoma	46	38	38	OS	indirectly	>60	qRT-PCR	7
Yang HF	2018	China	bladder cancer	102	51	51	-	-	-	qRT-PCR	8
Xie SP	2018	China	colorectal cancer	49	25	24	OS	indirectly	≤60	qRT-PCR	6
Shi HT	2017	China	esophageal squamous cell carcinoma	246	123	123	OS	directly	>60	qRT-PCR	8
Shi HT-1	2017	China	esophageal squamous cell carcinoma	152	76	76	OS	directly	>60	qRT-PCR	6
Nie FQ	2017	China	gastric cancer	54	27	27	OS	indirectly	≤60	qRT-PCR	7
Fang CY	2017	China	colonic cancer	73	36	37	-	-	-	qRT-PCR	7
Xia BR	2017	China	epithelial ovarian cancer	60	30	30	OS	indirectly	>60	qRT-PCR	7
Lv QL	2017	China	glioma	68	27	42	OS	directly	≤60	qRT-PCR	6
Tian FM	2016	China	non small cell lung cancer	173	85	88	OS	directly	>60	qRT-PCR	8
Wang WL	2016	China	colorectal cancer	159	79	80	OS	indirectly	>60	qRT-PCR	6
Li T	2015	China	hepatocellular carcinoma	113	57	56	-	-	-	qRT-PCR	7
Wang JS	2018	China	bladder cancer	172	-	-	OS	indirectly	≤60	qRT-PCR	7

Table 2 The association between ZFAS1 expression and clinicopathological features.

Clinicopathological features	studies	patients	OR (95%CI)	P-value	Heterogeneity	
					I-squared	P-value
Age (elderly vs young)	22	2122	1.06 (0.89, 1.26)	0.499	0.00%	0.604
Gender (male vs female)	20	2010	1.13 (0.94, 1.36)	0.209	19.50%	0.212
TNM stage (III+IV vs I + II)	18	1579	2.99 (1.97-4.54)	≤0.001	70.10%	≤0.001
Lymph node metastasis (present vs absent)	15	1034	2.67 (1.73-4.14)	≤0.001	65.50%	≤0.001
distant metastasis (present vs absent)	6	419	3.45 (1.61-7.39)	0.001	59.00%	0.032
Differentiation (poor vs well)	14	1490	1.57 (1.09-2.26)	0.015	56.80%	0.005
Tumor size (large vs small)	16	1494	1.54 (1.05-2.24)	0.025	65.30%	≤0.001