ORIGINAL ARTICLE

Low expression of LncRNA-CAF attributed to the high expression of HIF1A in esophageal squamous cell carcinoma and gastric cancer patients

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Abstract

Purpose Cancer-associated fibroblasts (CAFs) are major components of tumor microenvironment that stimulate ESCC and GC progression. The LncRNA-CAF, FLJ22447, is located in the vicinity of HIF1A, while their association remains unclear. This study aims to assess the FLJ22447 expression in the ESCC and GC patients and evaluate its association with the HIF1A gene.

Methods Fresh ESCC and GC tumor samples and their adjacent non-tumor tissues were collected from patients who underwent surgery in Imam Khomeini Hospital, Tehran, Iran. The expression of FLJ22447, HIF1A, and VEGF was evaluated using qRT-PCR test. The association of their expression with tumor clinicopathological features in ESCC patients was assessed. System biology tools were then applied for the possible biological subsequences of the FLJ22447.

Results A significant reduction in FLJ22447 expression was observed in ESCC and GC tissues than adjacent non-tumor tissues, while, the expression of HIF1A and VEGF were increased. Low expression of FLJ22447 was significantly correlated with HIF1A ($P = 2.4e{-}73$, R = 0.63) and VEGF ($P = 0.00019$, R = 0.15) expression. A significant relationship was detected between the high expression of HIF1A and tumor stages (I–II) and it was related to the reduced survival of ESCC patients. Conversely, increased VEGF expression was linked to the advanced stages (III–IV) and metastasis in ESCC. The analysis of FLJ22447-interacted proteins showed that MYC, JUN, SMRCA4, PPARG, AR, FOS, and CEBPA are the hub genes. These proteins were implicated in the cancer related pathways. Among them, SPI1, E2F1, TCF7L2, and STAT1 were significantly expressed in esophageal and gastric cancers that were functionally involved in the proliferation, apoptosis, and angiogenesis pathways in cancer.

Conclusion The results suggested that FLJ22447 may have a regulatory function on the HIF1A expression. We identified the FLJ22447-interacted proteins and their molecular function in cancer pathogenesis. Further research emphasis is to realize the association of FLJ22447 with its protein partners in progression of cancer. These may provide an insight into the FLJ22447 activity that could introduce it as a potential value in tumor gene therapy.

Keywords Cancer-associated fibroblasts · LncRNA · HIF1A · Esophageal cancer · Gastric cancer

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Introduction

Cancer disease is characterized by the genomic abnormalities which threaten the people's health worldwide. It has become the second leading cause of death after heart disease. Hypoxia and angiogenesis are known as common features of solid tumors [1, 2]. They are critical events for tumor cell growth and progression of cancer [3, 4]. Hypoxia is a key microenvironment condition that is modulated by transcription factors such as hypoxia-inducible factor 1 alpha (HIF1A). The HIF1A expression activates transcription of several genes that regulate proliferation of cell, metabolism of tumor cells, and angiogenesis processes [1, 5]. It is inhibited by the prolyl hydroxylase enzymes and the factor inhibiting HIF-1 oxygen sensors [6]. The HIF family members play an important role in the metabolism of cells in low oxygen condition. Previous research has documented the influence of HIF1A and HIF2A on the angiogenesis, cell metabolism, proliferation, and extracellular matrix remodeling [7].

Also, the HIF target genes influence all aspects of cancer biology including cell survival by TGF-β, bFGF, and p53 [8], metabolism via the GLUT-1 and glycolytic enzymes [9], and angiogenesis by the vascular endothelial growth factor (VEGF) [10]. In addition, the strong prognostic impact of the HIF1A and its association with the VEGF expression has been elucidated in pancreatic [11, 12] and breast [13] cancers.

Likewise, existing research recognizes the significant role played by the VEGF in angiogenesis in which promotes tumor growth and metastasis by blood vessels formation [14]. It is well known as an angiogenic factor that causes proliferation, migration, and permeability of endothelial cells. The high expression of VEGF causes to develop solid tumors by increasing the permeability of blood vessels and promoting angiogenesis [15]. The high expression of this gene also contributes to the other vascular diseases including neurodegeneration, retinal, and cancer [16].

Moreover, the impact of tumor microenvironment in cancer progression and metastasis has been demonstrated [17]. The cancer-associated fibroblasts (CAFs) are major components of tumor microenvironment that play a complex role in progression of cancer and are modulated by LncRNAs [18, 19]. Also, they can be formed upon stimulation of cytokines, growth factors, hypoxia, and non-coding RNAs [18]. The LncRNA-CAF, FLJ22447 (NR_039985), is recently identified in reprograming process of fibroblasts to mediate the growth of oral squamous cell carcinoma (OSCC) [19]. It is positioned on human chromosome 14q23 in the vicinity of the HIF1A gene. To date, the regulatory function of non-coding RNAs

(ncRNA) in the expression of neighboring genes have been widely reported [17, 20, 21]. However, the association of LncRNA-CAF in the expression of HIF1A remains unclear. Additionally, research on the FLJ22447 has been delimited to the RNA-seq data, in which this ncRNA was highly expressed in testicular, lung, thyroid, skin, and prostate tissues, respectively [22]. This study, therefore, was designed to assess the FLJ22447 expression in the esophageal squamous cell carcinoma (ESCC) and gastric cancer (GC) patients and evaluate its association with the HIF1A and the VEGF genes.

Materials and methods

Clinical samples

This research was officially permitted by the Research Ethics committee (IR.GOUMS.REC.1397.006) to perform on the patients undergoing surgical resection without adjuvant therapy from 2016 to 2017. The informed consent forms were received from participants by the Ethical Committee of Tumor Bank of Cancer Institute, Imam Khomeini Hospital, Tehran, Iran. The tissue samples of esophageal cancer (n = 40) and gastric cancer (n = 20) were instantly frozen in liquid nitrogen after surgery and stored at − 80 °C for further experiments. The margin of tumor tissue was histopathologically examined and considered as a non-tumor tissue.

RNA isolation and cDNA synthesis

In order to isolate the RNA of frozen tissues, TRIZOL reagent (Invitrogen, Life technology, USA) was used based on the manufacturer's directions. The quality and quantity of the isolated RNAs were measured by PicoDrop. The complementary DNAs were synthesized from the isolated RNA using Thermo Fisher Scientific cDNA synthesis kit and random hexamer primer according to the procedure.

Quantitative real-time PCR (qRT-PCR)

In order to examine the mRNA expression level of the FLJ22447, the HIF1A, and the VEGF, the qRT-PCR was performed using SYBER Green PCR master mix kit (TAKARA, Japan). The cDNA products were applied as templates for denaturing and annealing/extension steps at 95 °C and 60 °C, respectively. The melt curve analysis was performed for evaluating the specificity of PCR products. Table 1 presents the characteristics of primers applied in this assay, in which the GAPDH was considered as

Table 1 The characteristics of primers applied in the qRT-PCR expression analysis

Genes	Chromosomal location	Sequence 5′ to 3′	Amplicon size (bp)
HIF1A NM_181054.3	14q23	F: TCCAAGAAGCCCTAACGTGT R: TGATCGTCTGGCTGCTGTAA	180
VEGFA NM_001025366.2	6p21	F: ACTGCCATCCAATCGAGACC R: TCTCCTATGTGCTGGCCTTG	205
FLJ22447 NR_039985.1	14q23	F: AACCTCCTGAACAGCATCCA R:ACTGCACTCTGACTCAGCTT	308
GAPDH NM_002046.7	12p13	F: GGTGGTCTCCTCTGACTTCAACA R: GTTGCTGTAGCCAAATTCGTTGT	127

houdsekeeping gene. Ultimately, the fold change expression level of genes was calculated by the $2^{-\Delta\Delta CT}$ method.

Interaction analysis of FLJ22447

To identify the interaction of biological macromolecules with the FLJ22447, RNA association interaction database, the RAID v.2 database (www.rna-society.org/raid), was applied. The LncRNADisease (http://cmbi.bjmu.edu.cn/lncrnadisease) and the Lnc2Cancer (http://www.bio-bigdata.net/lnc2cancer) databases were screened out to investigate the biological function of irregular expression of the FLJ22447 in different types of cancer.

Systems biology analysis

The possible biological consequences of the FLJ22447 were determined by exploring the molecular mechanisms of its protein partners through the bioinformatics tools.

The protein–protein interaction network (PPI) of the predicted protein partners of the FLJ22447 was retrieved by the STRING (v 11.0) database with at least medium confidence (score 0.4). Then, the Cytoscape software was applied to identify the hub proteins by visualizing the protein interaction relationship network in network analyzer tool. The hub genes were subsequently recognized according to the degree parameter. Moreover, the functional annotation and significant pathways as a signature for predicting the clinical outcome were recognized by the PANTHER (v 14.0) and the KEGG resources, respectively.

Survival analysis

To assess whether the expression of HIF1A and VEGF is associated with the survival rate of patients with ESCA and STAD, the OncoLnc database (http://www.oncolnc.org/) was applied. The Kaplan–Meier analysis were performed for 72 ESCA patients and 189 STAD patients by the log rank comparison.

Statistical analysis

The statistical significance was determined using one-way analysis of variance (ANOVA) and Student's t-test by the SPSS software (V. 16). All data were presented as mean $\pm$ SD and the significant value of P was considered less than 0.05.

Fig. 1 The gene expression profile of FLJ22447, HIF1A, and VEGF in the ESCC and GC clinical samples. Comparison of FLJ22447, HIF1A, and VEGF expression in ESCC tumor tissues normalized to the housekeeping gene by $2^{-\Delta\Delta CT}$ method. Data are presented as fold change
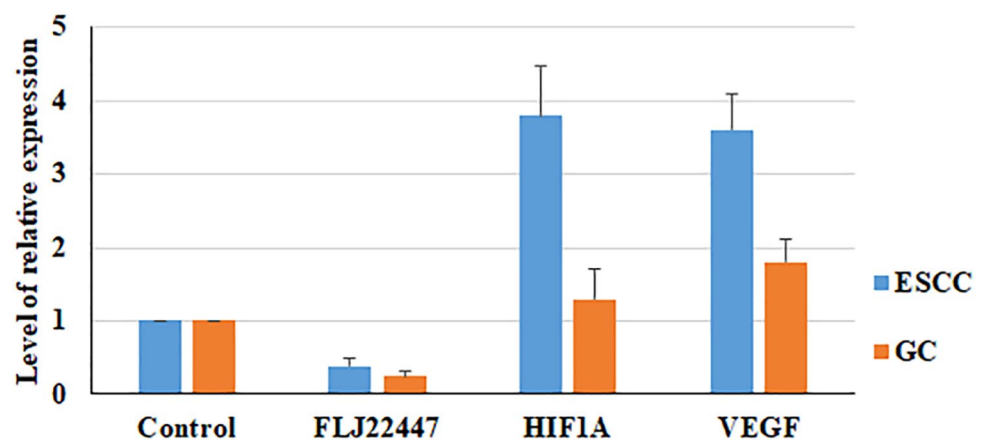
Table 2 Association of HIF1A expression with clinicopathological factors in ESCC

Clinical specify	Samples	HIF1A expression		P value
		High	Low	
Age				
60 <	16	7	9	.098
60 ≥	22	12	10	
Gender				
Male	21	10	11	.516
Female	17	8	9	
Tumor size (cm)				
5 <	20	10	10	.166
5 ≥	18	8	10	
Tumor stage				
I–II	11	7	4	.043*
III–IV	27	12	15	
Tumor grade				
I–II	8	3	5	.730
III–IV	30	15	15	
Metastasis				
Unknown	9	–	–	.531
Yes	10	5	5	
No	19	11	8	
Lymph node				
Yes	17	9	8	.261
No	21	9	12	
Total	38			

Table 3 Association of VEGFA expression with clinicopathological factors in ESCC

Clinical specify	Samples	VEGFA expression		P value
		High	Low	
Age				
60 <	16	8	8	.344
60 ≥	22	13	9	
Gender				
Male	21	11	10	.416
Female	17	7	10	
Tumor size(cm)				
5 <	20	10	10	.755
5 ≥	18	9	9	
Tumor stage I–II	11	7	4	.114
III–IV	27	12	15	
Tumor grade				
I–II	8	2	6	.002
III–IV	30	17	13	
Metastasis				
Unknown	9	–	–	
Yes	10	8	2	.023
No	19	10	9	
Lymph node				
Yes	17	9	8	.732
No	21	9	12	
Total	38			

Results

HIF1A expression in clinical ESCC and GC samples

The expression level of HIF1A was significantly increased in clinical ESCC specimens compared to the adjacent non-tumor tissues ($P < 0.05$, Fig. 1). No difference was observed in the HIF1A expression across GC samples and their adjacent non-tumor tissues ($P > 0.05$).

Table 2 represents the association of HIF1A expression with the clinicopathological factors in ESCC samples. A significant correlation was observed between the expression of HIF1A and tumor stage. The high expression of HIF1A was detected in stages I–II and its low expression in the stages III–IV.

FLJ22447 expression in clinical ESCC and GC samples

The expression of FLJ22447 was evaluated by qRT–PCR assay in the ESCC and the GC specimens. As can be seen in Fig. 1, the expression of FLJ22447 was significantly down-regulated in both ESCC and GC tissues than adjacent non-tumor tissues ($P < 0.05$).

VEGF expression in clinical ESCC and GC samples

The VEGF expression was significantly increased in both ESCC and GC samples than their adjacent non-tumor tissues ($P < 0.05$, Fig. 1). Table 3 shows the association of the VEGF expression with the clinicopathological features of the ESCC patients. A remarkable link was recognized between the high expression of VEGF and advanced stages (III–IV) and metastasis ($P < 0.05$).

In silico *expression profile of FLJ22447, HIF1A, and VEGF*

The expression pattern of target genes in esophagus (ESCA) and stomach (STAD) carcinomas samples was explored by the GEPIA database (Fig. 2A). The FLJ22447 was highly expressed in ESCC than STAD. However,
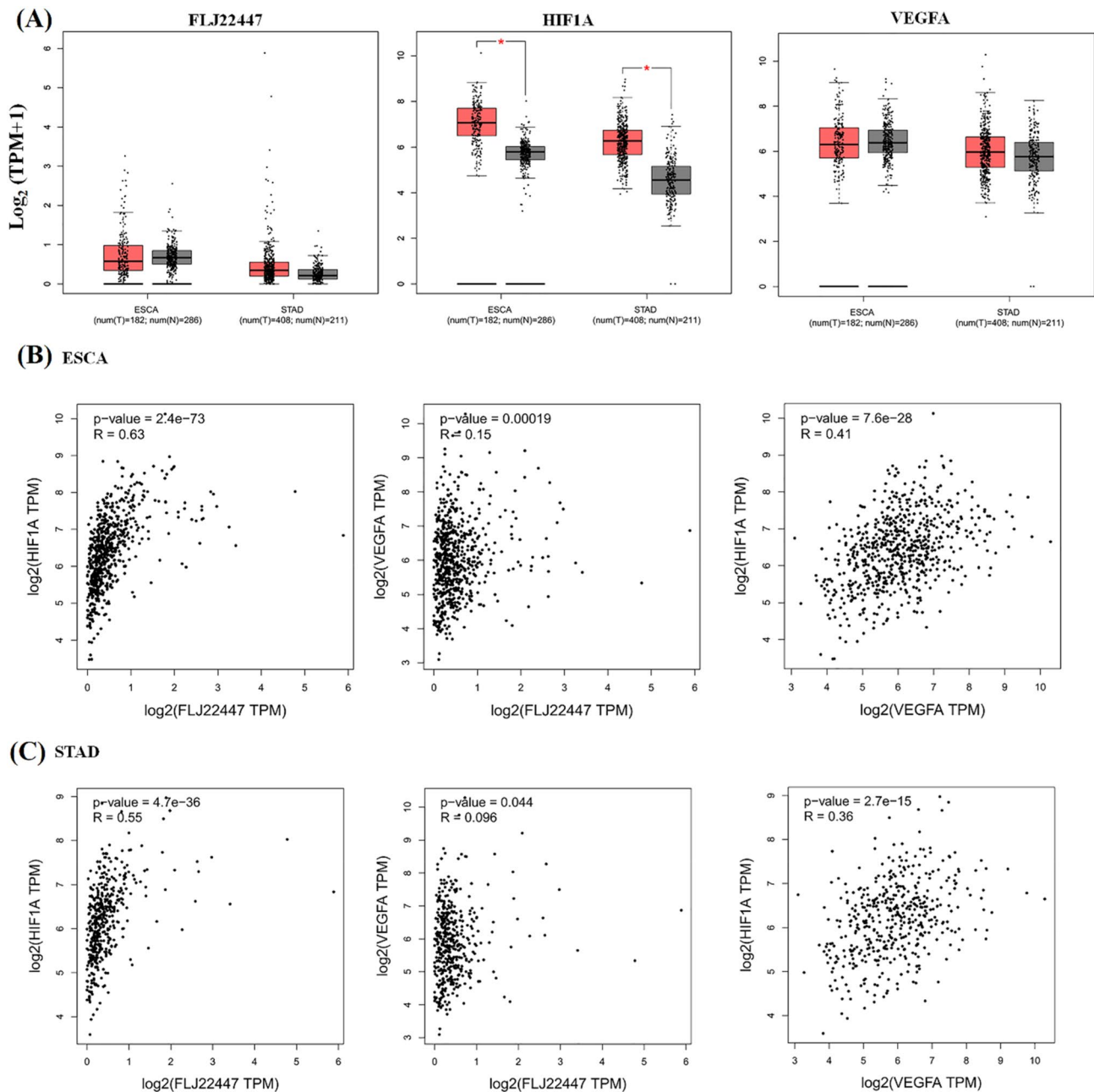
Fig. 2 Comparison of the expression profile of FLJ22447, HIF1A, and VEGF in ESCA and STAD carcinoma. **A** The RNA seq data in GEPIA indicated that the expression of HIF1A was increased in ESCA tissues than normal tissues. In contrast, the mean expressions of VEGF and FLJ22447 were lower than in ESCA tissues. **B** Correlation of FLJ22447, HIF1A, and VEGF gene expression in both ESCA and STAD were considered. The analysis of spearman correlation revealed that low expression of FLJ22447 was significantly correlated with the HIF1A and the VEGF expression in esophagus and stom-ach carcinomas, respectively. Additionally, a positive correlation was observed between the HIF1A and the VEGF genes in both carcinomas. **C** The Kaplan-Meier survival curves for the patients harboring ESCC and STAD with regard to high and low expression of HIF1A and VEGF are demonstrated. Patients with high HIF1A expression have less survival. Data adopted from GEPIA resources. Log_2 (TPM + 1) was used for log-scale. *ESCA* esophageal carcinoma; *TPM* Transcripts per million

in comparison with the adjacent non-tumor tissues, its expression reduced in ESCC, whereas, increased in STAD. Interestingly, the transcription of HIF1A was significantly heightened in both ESCA and STAD than their adjacent non-tumor tissues ($P < 0.05$). The mean expression of the VEGF and the FLJ22447 in ESCA were lower than the adjacent non-tumor ones.
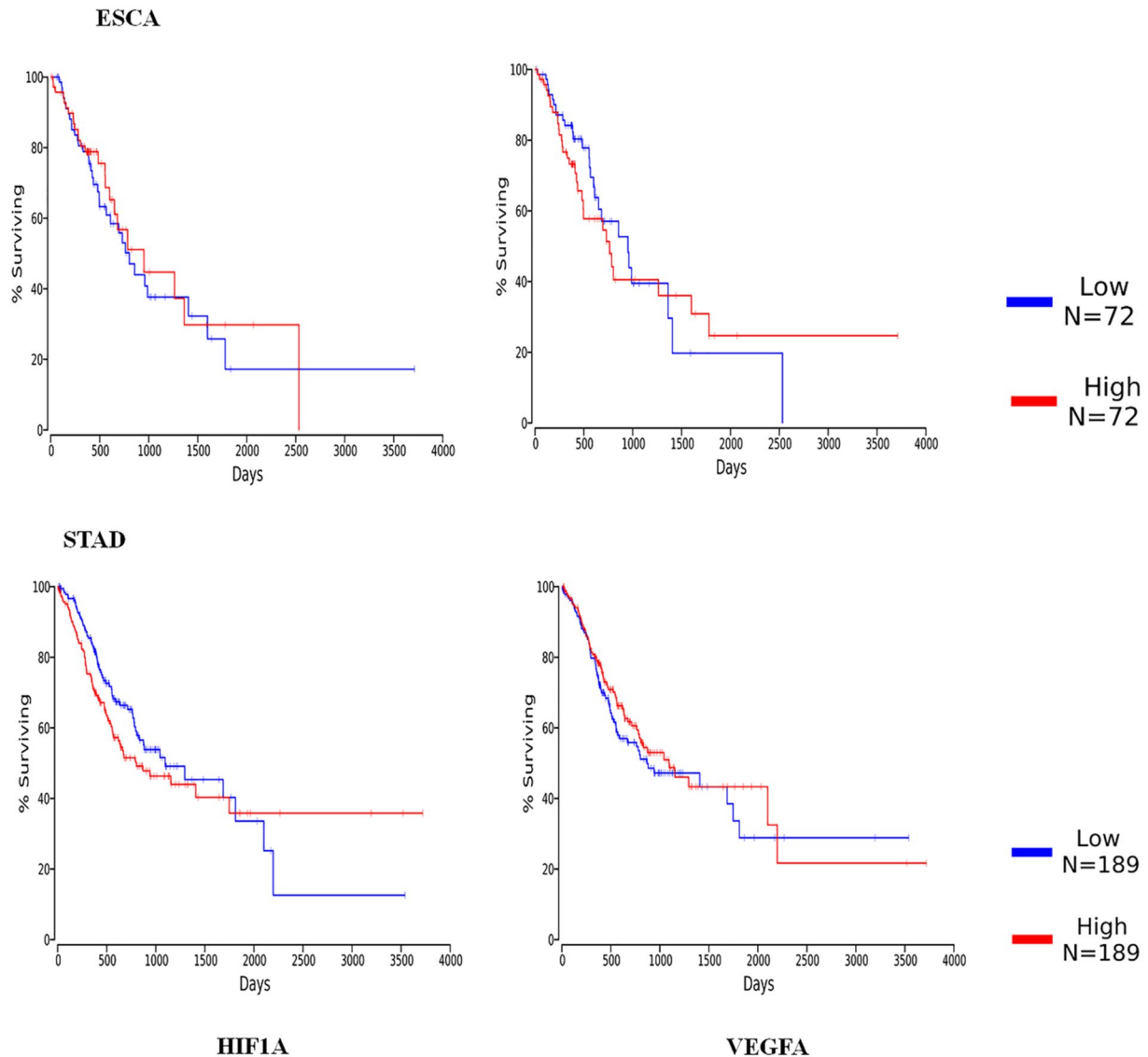
Fig. 3 Kaplan–Meier survival curves for the patients harboring ESCA and STAD with regard to high and low expression of HIF1A and VEGF. Patients with high HIF1A expression have less survival

Moreover, down-regulation of the FLJ22447 in esophagus and stomach carcinomas was significantly correlated with the HIF1A ($P = 2.4e–73$, R = 0.63; $P = 4.7e–36$, R = 0.55) and the VEGF ($P = 0.00019$, R = 0.15; $P = 0.044$, R = 0.096) expression, respectively (Fig. 2B, C). Also, a positive correlation was observed between the HIF1A and the VEGF genes in esophagus and stomach carcinomas ($p = 7.6e–28$, R = 0.41; $p = 2.7e–15$, R = 0.36).

Patients' survival analysis

Figure 3 illustrates the survival rate of patients with high vs low expression levels of VEGF and HIF1A. The Kaplan–Meier survival curve indicated that 10-years survival rate of ESCA and STAD patients was approximately 30%. No significant difference was observed in terms of high and low expression of HIF1A and VEGF with the outcome of ESCA and STAD patients. The analysis of patients' survival showed that the ESCA patients with low expression of HIF1A achieved better survival than those with high expression.

Interaction analysis of FLJ22447 in human tumors

The term of sequence ontology for the FLJ22447 is sense_intronic_ncRNA in the LNCipedia database.

Table 4 The FLJ22447 interaction with proteins and RNAs molecules

Protein	FOXH1, BATF, AR, SPI1, FOS, BRF1, SMARCC2, JUN, POU2F2, JUND, SP1, CEBPB, E2F1, TCF12, TAF1, MAX, NANOG, NRF1, SMARCA4, TCF7L2, E2F4, PPARG, SMARCB1, CEBPA, MYC, SMARCC1, RAD21, HNF4A, BCL11A, EBF1, STAT1
MicroRNA	let-7e-5p, let-7f-5p, miR-302d-3p, miR-302c-3p, miR-200b-3p, miR-204-5p, miR-15a-5p, miR-302a-3p, miR-15b-5p, miR-144-3p, miR-421, miR-216a-5p, miR-302b-3p, miR-455-5p, miR-135b-5p, miR-410-3p, let-7g-5p, miR-155-5p, miR-16-5p, miR-216b-5p, miR-107,miR-205-5p, miR-424-5p, miR-433-3p, miR-103a-3p, miR-135a-5p, miR-154-5p, miR-539-5p, miR-497-5p, miR-195-5p, let-7i-5p, let-7b-5p, miR-98-5p, miR-153-3p, miR-211-5p, miR-544a

The interaction of ncRNA FLJ22447 with other macromolecules have been predicted by the RAID v2.0 resource. According to the GEPIA, the expression of SPI1, E2F1, TCF7L2, STAT1 genes were significantly higher than the non-tumor tissue in ESCA and STAD
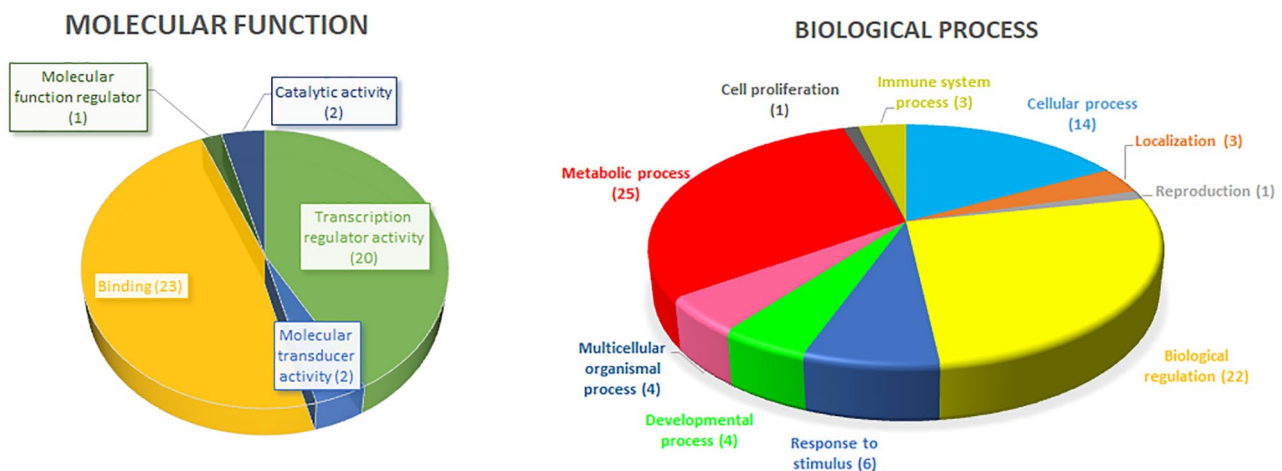
Fig. 4 GO enrichment analysis of FLJ22447-interacted proteins. Molecular function and biological process classifications of FLJ22447 interacted proteins were depicted in pie chart format. Data retrieved from PANTHER-Gene list analysis (v14.0)

It contains three transcripts with the length of 1368, 1312, and 577 bp. According to the LncRNA Disease database, the impact of FLJ22447 in cervical, lymphoma, glioma, stomach, thyroid, and bladder cancers has been predicted through the TAM method. Also, the interaction of FLJ22447 with 67 protein coding-genes and RNAs was revealed in the RAID v.2 resource (Table 4). These predicted results provide important insights into FLJ22447 function in the processes of biologic. However, further research is demanded.

Enrichment analysis of interacted proteins with FLJ22447

Molecular function and biological process of the FLJ22447-interacted proteins were explored by the PANTHER database

(Fig. 4). The enrichment analysis suggested that 23 and 20 genes participate in two major molecular function categories including binding (GO: 0005488; 47.9%) and transcription regulator activity (GO: 0140110; 41.7%), respectively. From the pie chart above, we can see that these proteins were mostly involved in metabolic process (GO: 0008152; 30.1%), biological regulation (GO: 0065007; 26.5%), and cellular process (GO: 0009987; 16.9%).

Further, the conceivable biological function of FLJ22447 was demonstrated by finding the most important nodes across its interaction protein partners (Fig. 5A). Using network analyzer tool of Cytoscape, MYC (24), JUN (21), SMRCA4 (20), PPARG (18), AR (17), FOS (17) and CEBPA (16) protein-coding genes were detected as the hub genes according to the degree method (Fig. 5B). According to the network analysis

Fig. 5 Functional classification of FLJ22447-interacted proteins. **A** The molecular action mode of FLJ22447 protein partners with medium score (0.4) was nominated by STRING (V 11.0). The line colors indicate binding (blue), activation (green), inhibition (red), reaction (black), post-translational modification (pink), and transcriptional regulation (green mint). The un-specified, positive and negative effects were illustrated by dot, arrowhead, and bar, respectively. **B** Network of FLJ22447-interacted proteins was constructed

by application of CytoHubba in Cytoscape software. **C** The network of hub genes was depicted according to the degree method. MYC, JUN, SMRCA4, PPARG, AR, FOS and CEBPA protein-coding genes were identified as the hub genes. D The clustergram of KEGG 2019 human pathway section in Enrichr demonstrated that these proteins were involved in thyroid cancer, acute myeloid leukemia, colorectal, and breast cancers. It is interesting to note that all the hub genes were involved in pathways in cancer (map05200). (Color figure online)

of the hub genes, MYC and AR mostly act as an activator of other hub genes. While, PPARG and CEBPB are activated by others (Fig. 5C). Moreover, the result of Enrichr analysis revealed that these proteins were implicated in thyroid cancer (PPARG, MYC), acute myeloid leukemia (MYC, CEBPA), colorectal and breast cancers (MYC, JUN, FOS) (Fig. 5D). As shown in the above figure, all the hub genes were involved in the cancer related pathways (map05200).

Discussion

Prior researches have noted that tumor microenvironment particularly its major component CAFs promote ESCC and GC initiation and progression [23, 24]. Among the components of the CAFs, the functional impact of noncoding RNAs has been recently considered in cancer biology. The lncRNAs participate in tumor-stromal crosstalk and provide a suitable tumor microenvironment [25]. The FLJ22447, referred to LncRNA-CAF, was introduced

as a reprogramming factor of CAF in OSCC [19]. This lncRNA is cytologically located in the vicinity of HIF1A. Nevertheless, very little was found on the association of FLJJ22447 with the HIF1A and VEGF. Consequently, the present study was set out to identify whether the FLJJ22447 expression level can influence the vicinity gene expression of HIF1A in the ESCC and GC patients.

Our data showed that the FLJJ22447 was lower expressed in the human ESCC and GC. The interesting point of expression assay was that the most notable reduction in the FLJJ22447 expression was observed in ESCC samples; at the same condition that the expression of HIF1A increased. The value of FLJJ22447 suggests that it could be a major factor, if not the only one, regulating its neighbor gene, HIF1A.

These findings further support the idea of FLJJ22447 involvement into the cancer-associated pathways through the enrichment analysis of FLJ22447-interacted protein-coding genes (Fig. 5A). We also identified that MYC, JUN, SMRCA4, PPARG, AR, FOS and CEBPA genes as critical

Fig. 6 Expression profile analysis of the FLJ22447-interacted proteins. **A** Among the FLJ22447-interacted proteins, SPI1, E2F1, TCF7L2, and STAT1 genes were significantly expressed than non-tumor tissue in ESCA and STAD. **B** They contribute in proliferation, evading apoptosis, and sustained angiogenesis pathways in cancer (hsa05200). Data retrieved from the GEPIA, KEGG, and Enrichr databases

nodes that take part in pathways of thyroid, colorectal, and breast cancers (Fig. 5D). Additionally, functional interactions network of these proteins suggested that MYC and AR genes act as an activator in this biological network (Fig. 5C).

The underlying biological mechanisms of FLJJ22447 have not been fully elucidated. It has been demonstrated that the FLJJ22447 increased the IL-33 stability by preventing autophagic degradation and promotes tumor proliferation [18]. They also mentioned that the FLJ22447 promotes CAF activation and tumor progression in OSCC. Moreover, high expression of FLJ22447 was associated with a high TNM stage and poor patient survival, suggesting it as a novel therapeutic target in OSCC [19].

Assessment of RNA-seq data in the GEPIA revealed that the expression of SPI1, E2F1, TCF7L2, and STAT1 genes among the FLJ22447-interacted proteins were significantly higher than non-tumor tissue in ESCA and STAD (Fig. 6). They contribute in proliferation, evading apoptosis, and sustained angiogenesis pathways in cancer (hsa05200). From the oncology point of view, the over-expression of these genes is contributed to the tumor progression. The SPI1 and E2F1 are known as oncogenic transcription factors [26]. It is possible that the FLJ22447 expression in ESCC and GC is associated with these genes, at least in part. Further research on the current topic are therefore recommended. These

results indicated that the FLJ22447 may have several biological functions and participate in cancer-associated pathways, suggesting its potential value in tumor gene therapy.

We have also found a positive link between the HIF1A and VEGF expression in ESCC tissues than adjacent non-tumor tissues. This result is consistent with other studies who suggested that these two angiogenic factors are essential in progression of squamous cell carcinoma of the esophagus [27–29].

In addition, HIF1A acts as a transcription factor for the VEGF [28]. In fact, there is a HIF1A binding site in the VEGF promoter that results in the regulating of the VEGF expression during hypoxia [27, 30].

In terms of clinical view, the correlation of these angiogenic factors with the histopathological parameters in breast cancer, pancreatic adenocarcinoma, and esophagus carcinoma has been demonstrated [2, 12, 28].

We found that low expression of HIF1A was related to the tumor stage, however, this association was not previously reported in ESCC tumor specimens [27]. Whereas, they demonstrated a correlation among high expression of HIF1A and venous invasion.

From this point of vision, increased expression of the VEGF in the present study was associated with high tumor grade (III–IV) and metastasis. In accordance with this result,

previous researches have demonstrated that the VEGF expression was correlated with tumor stage in ESCC and gastric adenocarcinoma [29, 31]. The association of these molecules with tumor grade, metastasis, and vascular invasion suggested their contribution to the survival of tumor cells. HIF1A and VEGF are important determinants of hypoxia and angiogenesis phenomena in cancer [18, 32]. Recently, their implication in CAFs through lncRNAs, tumor suppressor genes, and oncogenes have been demonstrated [33, 34].

With respect to the survival rate of ESCA and STAD patients, there were no significant differences in terms of high and low expression of HIF1A and VEGF. However, high expression of VEGF in patients with gastric adenocarcinoma indicated a poor prognosis for overall survival [31]. The same result has been reported in the patients harboring breast cancer and ESCC with high expression of HIF1A [27, 35].

Conclusion

This investigation purposed to determine the association of FLJ22447 with the HIF1A as its neighbor gene in the ESCC and GC patients. Herein, we demonstrated low expression of FLJ22447 in the patients with ESCC and GC that was linked to the HIF1A expression. It is possible, therefore, that the vicinity of HIF1A with FLJ22447 may affect the regulation of its expression. Also, the relationship between HIF1A and VEGF was demonstrated in the ESCC and GC patients. The enrichment analysis of FLJ22447-interacted proteins revealed that this ncRNA may have various roles in the biological processes and may be involved in the pathways attributed to the cancer. Association of the oncogenic transcription factors with the FLJ22447 and their contribution in proliferation, evading apoptosis, and sustained angiogenesis pathways in cancer, suggesting its potential value in tumor gene therapy. Notwithstanding our research limitations, this study provides insights into the FLJ22447 interactions and its protein partners.

Declarations

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