The Diagnostic Value of LGALS1 in Esophageal Cancer and its Potential Molecular Pathways via Bioinformatic Analysis

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Research article

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Abstract

Background: Esophageal cancer is one of the most common malignant tumors. The purpose of this study was to reveal the expression of LGALS1 in esophagus cancer (ESCA) and its clinical value, and to explore the mechanism of LGALS1 in the occurrence and development of ESCA.

Methods: Oncomine, Tumor Immune Estimation Resource (TIMER) and The Cancer Genome Atlas (TCGA) database were used to analyze the expression of LGALS1 in ESCA and its value in the diagnosis of ESCA. The correlation between LGALS1 and the clinicopathological characteristics of ESCA patients was analyzed in the Ualcan database. In TCGA database, we performed Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), and Gene Set Enrichment Analysis (GSEA) to elucidate the potential mechanism underlying the role of LGALS1 in ESCA. LGALS1 co-expressed genes were imported into the STRING database to build a protein-protein interaction (PPI) network. The CytoHubba plug-in in Cytoscape was used to screen the hub gene and was verified in Gene Expression Profiling Interactive Analysis (GEPIA) and TCGA database.

Results: LGALS1 was highly expressed in ESCA tissues. Increasing the expression level of LGALS1 was related to age, ethnicity, clinical stage, tumor grade, and histological subtype of ESCA patients, and receiver operating characteristic (ROC) analysis showed that the area under the curve (AUC) was 0.8511 ($P < 0.001$). There are 482 LGALS1 co-expressed genes. GO and KEGG show that LGALS1 co-expressed genes are mainly involved in endothelial cell differentiation, transforming growth factor receptor signaling pathway, epithelial cell proliferation, ECM receptor interactions, leukocyte migration, transcriptional disorders during cancer, PI3K/AKT signaling pathway and other processes. GSEA showed that elevated LGALS1 was mainly enriched for ECM receptor interactions, cancer pathways, and TGF BETA signaling pathways. The Hub genes COL1A1, FN1, COL1A2, COL3A1, COL5A1, COL5A2, COL4A2, COL18A1, and COL6A1 are higher expressed in ESCA tissues and have diagnostic significance in ESCA.

Conclusion: LGALS1 expression is elevated in ESCA patients and may be a potential diagnostic marker for ESCA patients. PI3K/AKT signaling pathway, TGF BETA signaling pathway, cancer pathway, cytokine and cytokine interaction may be an important pathway for regulation in occurrence and development of ESCA.

Background

ESCA is one of the common malignant tumors, and the cancer-related mortality ranks among the top 10 [1–3]. Worldwide, the incidence and mortality of ESCA patients are similar, with 572,034 (3%) new cases and 508,585 (5.3%) deaths [2]. In China, the number of ESCA cases is 477,900, of which 320,800 are male cases, 157,200 are female cases; 375,000 deaths are among them, 253,800 male deaths and 121,300 female deaths [3]. With the development of surgical methods, chemotherapy, radiotherapy and other treatment methods, the prognosis of ESCA patients has been improved [4–6]. However, the 5-year overall survival (OS) of ESCA patients is still low [7]. Therefore, it is of great significance to find new treatments for ESCA and explore the molecular mechanisms of their development.

LGALS1, also known as Galectin-1 (Gal1), has increased expression in human malignant tumors such as liver cancer, ovarian cancer, schwannoma, and gastric cancer [8–11], and is associated with the prognosis of patients with malignant tumors such as gastric cancer, bladder urothelial carcinoma, and gingival squamous cell carcinoma [11–13]. LGALS1 is highly expressed in cervical cancer tissues and cells. Increasing the expression of LGALS1 significantly promotes cervical cancer cell proliferation, inhibits apoptosis, and significantly enhances cell migration and invasion capabilities. Interference with LGALS1 expression has the opposite effect [14]. Galectin-1 is highly expressed in the stroma of pancreatic ductal adenocarcinoma. Galectin-1 overexpression promotes cancer cell proliferation, migration, and invasion [15]. Galectin-1 expression was increased in gastric cancer tissues, and Increased Galectin-1 expression is associated with poor prognosis in patients with gastric cancer. Galectin-1 overexpression can induce EMT, migration and invasion of gastric cancer cells [11]. In addition, increasing Galectin-1 expression may be an independent factor for the prognosis of bladder cancer [12]. In summary, LGALS1 expression is elevated in many malignancies, and the expression level of LGALS1 is related to the occurrence and development and poor prognosis of malignant tumors, which indicates that LGALS1 may be a potential target in tumor diagnosis and treatment. However, the role and potential value of LGALS1 in ESCA have not been reported in the literature. Therefore, the purpose of this study was to analyze the expression of LGALS1 in ESCA and its clinical significance, and to explore the role of LGALS1 in the development of ESCA and its possible regulatory mechanisms.

Materials And Methods

Oncomine Database

Oncomine (<https://www.oncomine.org/>) database is a gene chip-based database and integrated data mining platform [16]. The Oncomine database was used to set screening conditions to explore the expression of single genes in cancer. In this study, we set the screening thresholds as: 1) Gene: LGALS1; 2) Comparison type: Cancer vs. Normal; 3) Data type: mRNA; 4) Simple type: Clinical specimen; 5) Threshold setting conditions ($P < 0.001$, Fold change 1.5, Gene rank = All).

TCGA database mRNA data download

Download gene expression data of type ESCA HTSeq-FPKM from the TCGA (<https://portal.gdc.cancer.gov/>) website, including 11 cases of normal esophageal normal tissue and 160 cases of esophageal cancer tissue. The TCGA database was sorted and extracted to verify the expression of LGALS1 and Hub genes in the TCGA database and explore its value in the diagnosis of ESCA patients.

Ualcan and GEPIA databases

According to Ualcan (<http://ualcan.path.uab.edu/index.html>) RNA-seq and ESCA type clinical data, the expression level of LGALS1 mRNA in normal esophageal tissue and ESCA tissue was analyzed, and its relationship with the clinicopathological characteristics of ESCA patients [17]. The GEPIA database is a database that organizes TCGA data and performs secondary analysis. The correlation between LGALS1 and Hub genes was verified in GEPIA (<http://gepia.cancer-pku.cn/>) [18].

Screening for LGALS1 co-expressed genes

In this study, the Pearson correlation coefficient was selected to represent the association between genes. The Pearson correlation coefficient can be used to represent the biological relationship between two genes in numerical form. R was used to screen LGALS1-related co-expressed genes in the TCGA database. Screening thresholds: $|r| > 0.5$ and $P < 0.001$.

GO and KEGG analysis

In order to explore the biological functions involved in LGALS1 and the mechanisms that regulate ESCA progression, we performed GO annotation and KEGG analysis on LGALS1 co-expressed genes. GO annotations include biological processes (BP), molecular functions (MF), and cellular components (CC). GO annotation and KEGG analysis of LGALS1 co-expressed genes were performed using R to screen for humans and $P < 0.05$. GSEA is a method to reveal genomic expression data through basic knowledge. The TCGA gene expression data set was divided into high and low expression groups based on the median expression level of LGALS1. The effect of high and low expression levels of LGALS1 on each gene was analyzed using GSEA version 4.01, and the related mechanism of LGALS1 participation in ESCA progress was further analyzed. The genome was permuted 1000 times per analysis. LGALS1 expression level is used as a phenotypic marker. Nominal p-values and Nominal enrichment scores (NES) were used to classify enrichment pathways in each phenotype [19].

PPI network construction and hub gene analysis

The online STRING (<https://string-db.org/>) database was used to analyze the PPI network relationship of LGALS1 co-expressed genes to show the role relationship of LGALS1 co-expressed genes in ESCA. The combined score > 0.7 was considered a statistically significant difference. The obtained PPI network is imported into Cytoscape 3.6.1 software. Highly connected nodes are very important to maintain the stability of the entire PPI network. Therefore, the top 10 genes screened by the CytoHubba plug-in are defined as the hub genes in the PPI network [20], and Further analyze the clinical value of the Hub gene in the TCGA database to explore the role of LGALS1 in ESCA.

Statistical analysis

Data processing was performed using perl and R (v.3.5.2), Wilcoxon rank sum was used to test the expression of LGALS1 in ESCA. ROC was used to analyze the diagnostic value of LGALS1 and its hub gene in ESCA. Pearson correlation analysis screened LGALS1 co-expressed genes.

Results

LGALS1 is abnormally expressed in cancer tissues

In the Oncomine database, LGALS1 expression has increased in tissues of nervous system tumors, breast cancer, cervical cancer, colorectal cancer, ESCA, gastric cancer, head and neck cancer, kidney cancer, and leukemia, while the expression in bladder cancer, cervical cancer, leukemia, lung cancer, prostate cancer and other tissues decreased (Fig. 1A). In addition, LGALS1 expression was up-regulated in cholangiocarcinoma (CHOL), ESCA, head and neck squamous cell carcinoma (HNSC), Kidney renal clear cell carcinoma (KIRC), Liver hepatocellular carcinoma (LIHC) and other tumor tissues, while it decreased in breast invasive carcinoma (BRCA), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC) and other tumor tissues in Timer database (Fig. 1B, $P < 0.05$).

Expression of LGALS1 and its diagnostic value in ESCA

In addition, LGALS1 was elevated in ESCA and its subtypes (Table 1 and Fig. 2). In Oncomine database, Hao and Kim found that LGALS1 expression was elevated in esophageal adenocarcinoma compared with esophageal tissue ($P < 0.05$). Hu and Su found that LGALS1 expression was elevated in esophageal squamous cell carcinoma compared with esophageal tissue ($P < 0.05$). Kim also found that LGALS1 expression was higher in Barrett’s esophagus than in normal esophageal tissues ($P < 0.05$). In the TCGA database, LGALS1 expression was elevated in ESCA tissue compared to esophageal tissue, and ROC analysis showed $AUC = 0.8511$ (Fig. 2, $P < 0.001$).

Table 1
LGALS1 expression in esophageal cancer tissue in Oncomine database.

	ESCA vs. Normal	Fold change	t-test	p-value	Ref
LGALS1	Esophageal Adenocarcinoma vs. Normal	11.066	7.781	4.32E-6	Hao
	Esophageal Adenocarcinoma vs. Normal	4.481	8.571	6.95E-14	Kim
	Barrett’s Esophagus vs. Normal	2.004	3.860	3.28E-4	Kim
	esophageal squamous carcinoma vs. Normal	3.850	5.694	1.64E-6	Hu
	esophageal squamous carcinoma vs. Normal	1.905	5.039	1.06E-6	Su

Increased expression of LGALS1 is associated with the clinicopathological characteristics of ESCA patients

In Ualcan database, we found that LGALS1 expression levels correlate with the clinicopathological characteristics of ESCA patients (Fig. 3). In detail, the expression level of LGALS1 is related to the age of ESCA patients (41–60 years vs 61–80 years), ethnicity (Caucasian vs Asian; African American vs Asian), weight (Normal_Weight vs Extreme_Weight; Normal_Weight vs Obese; Normal_Weight vs Extreme_Obese; Extreme_Weight vs Extreme_Obese; Obese vs Extreme_Obese), smoking history (Non smoker vs Reformed smoker1), cancer stage (Stage1 vs Stage2; Stage1 vs Stage3), tumor grade (Grade 2 vs Grade 3), histological subtype (Adenocarcinoma vs Squamous -cell-carcinoma) and lymph node metastasis (N0 vs N1; N0 vs N2) (Fig. 3, $P < 0.05$).

LGALS1 co-expressed genes

ESCA mRNA expression data was downloaded using the TCGA public database, and 482 genes of LGALS1 with moderate or higher levels were screened, of which 349 were positively correlated (Table 2) and 133 were negatively correlated (Table 3). The top 10 genes that are positively and negatively correlated with LGALS1 co-expressed genes are shown in Fig. 4.

Table 2
LGALS1 positively related genes.

Gene	Cor	Gene	Cor	Gene	Cor	Gene	Cor	Gene	Cor	Gene	Cor	Gene
COL6A2	0.816	ADAMTS12	0.677	MMP11	0.629	COL7A1	0.595	GJA1	0.565	SGTB	0.541	RNF122
EMP3	0.804	GAS1	0.677	P4HA3	0.629	CAV2	0.595	CHSY3	0.564	PACS1	0.541	NINJ1
TNFAIP6	0.8	ADAM12	0.675	SULF1	0.628	LOX	0.595	MAPK11	0.564	RILPL1	0.54	HK3
CERCAM	0.797	RAB31	0.675	CHST11	0.626	SLC39A13	0.593	AMIGO2	0.564	OSCAR	0.539	PTHLH
COL5A1	0.791	ADAMTS2	0.673	VEGFC	0.626	VKORC1	0.593	HHIPL1	0.563	LHFPL6	0.539	PLS3
BGN	0.787	EVA1B	0.673	CHST15	0.625	HCFC1R1	0.593	PDGFC	0.563	THBS1	0.538	FAM89B
COL1A1	0.784	MSN	0.672	SNAI2	0.625	FHL3	0.592	CD14	0.562	COLGALT1	0.538	CNGB1
COL1A2	0.781	CAV1	0.671	CD276	0.625	FCGR2A	0.592	GNAI2	0.562	SELENOM	0.538	TUBB6
COL6A1	0.78	GLT8D2	0.669	SPOCK1	0.623	NCS1	0.591	AGTRAP	0.56	ISM1	0.538	MSR1
INHBA	0.775	LUM	0.668	EHD2	0.623	MEIS3	0.591	SERPINF1	0.56	GUCY1A1	0.538	FBN1
CLEC11A	0.765	PLAU	0.668	TMEM200B	0.623	TSPAN4	0.591	FJX1	0.56	COL18A1	0.537	RTN4
MFAP2	0.759	PODNL1	0.668	P4HA2	0.623	FLNA	0.59	PIK3CD	0.56	RFTN1	0.536	PLXDC1
COL3A1	0.75	POSTN	0.667	PLOD1	0.623	HAS2	0.589	WDR54	0.56	CYP27C1	0.535	MN1
CMTM3	0.747	GFPT2	0.666	SERPINH1	0.621	ARL4C	0.588	RARRES2	0.559	DZIP1	0.535	AIF1
COL5A2	0.745	MMP2	0.666	FSTL3	0.618	AXL	0.587	FBLN2	0.559	FLRT2	0.535	MMP17
PPP1R18	0.742	CAVIN3	0.665	PRNP	0.618	SHISAL1	0.587	DCBLD1	0.559	ASAP1	0.535	PDLIM4
ITGA5	0.74	TWIST2	0.665	GLI3	0.617	BASP1	0.586	PRRX2	0.558	CCDC8	0.535	MT2A
FAP	0.738	P3H1	0.664	CDH11	0.617	QKI	0.585	HAPLN3	0.558	TYROBP	0.535	WNT2
VIM	0.733	CLMP	0.663	GLIS1	0.615	ARSI	0.584	KDELC1	0.558	GXYLT2	0.534	FADS3
PDPN	0.733	GPR68	0.663	C1R	0.615	SPON2	0.582	GUCY1B1	0.558	SNAPC2	0.534	ELOVL5
PRRX1	0.731	CPXM1	0.662	NLGN2	0.614	C1S	0.581	BEND6	0.558	BICC1	0.533	S100A3
PCOLCE	0.73	TWIST1	0.661	COL16A1	0.614	ANGPTL2	0.581	PXDN	0.557	WIPF1	0.533	C8orf58
TGFB1	0.729	DKK3	0.661	MXRA8	0.613	SMIM3	0.581	DENND5A	0.557	NXN	0.532	P3H3
KIRREL1	0.726	HOMER3	0.66	S1PR2	0.612	SNAPC1	0.581	FHOD3	0.557	MAPK12	0.532	KLHL5
COL5A3	0.725	COL12A1	0.659	CD248	0.612	GALNT18	0.58	FIBIN	0.556	RUNX2	0.532	THSD1
HTRA3	0.724	ACTN1	0.658	OLFM2	0.611	TIMP2	0.579	GGT5	0.556	FOXC2	0.531	FRMD6
THY1	0.722	PGF	0.657	GLIPR1	0.611	CDC42EP3	0.579	COL27A1	0.555	COL4A2	0.53	CORO6
SCARF2	0.722	EDNRA	0.657	MMP13	0.61	APCDD1L	0.578	NNMT	0.555	SIRPA	0.53	SPSB1
PDLIM7	0.719	MARVELD1	0.655	SLC12A4	0.609	GPSM1	0.576	PDCD1LG2	0.553	SRPX	0.53	IFI27L2
LOXL2	0.715	GNB4	0.654	ANXA5	0.609	TUBA1A	0.576	EMILIN1	0.553	FNDC1	0.529	MAP7D1
MMP14	0.714	SERPINE1	0.647	IGFBP7	0.608	LTBP2	0.576	TGFB3	0.552	GNA12	0.529	MED10
IKBIP	0.712	CHN1	0.647	UCN2	0.608	ITGA11	0.576	NRP2	0.551	MAP7D3	0.529	FAM20C
FN1	0.711	PLPP4	0.647	WISP1	0.607	FCGR3A	0.575	MYH9	0.55	CD109	0.529	GJC1
CTHRC1	0.711	NOX4	0.645	CSGALNACT2	0.606	LTBP1	0.574	HDGFL3	0.55	SPI1	0.528	P4HA1
BMP1	0.705	HTRA1	0.644	TGFB1	0.606	EVC	0.573	LRRC17	0.549	KIAA0930	0.528	COLEC12
SPARC	0.704	ANTXR1	0.643	FSCN1	0.605	GPX7	0.573	ICAM5	0.549	DAPK3	0.528	ST6GALNAC
CAVIN1	0.699	MFGE8	0.642	MSANTD3	0.605	GLIPR2	0.572	EVA1A	0.548	NRM	0.527	CYR61
GPX8	0.694	RCN3	0.641	NTM	0.603	MSC	0.571	TREM2	0.548	LRP12	0.527	DCBLD2
SUGCT	0.693	COL11A1	0.641	COPZ2	0.601	CCDC102A	0.57	DRAP1	0.548	MAFB	0.526	CORO1C
CTSK	0.688	SFRP2	0.64	TGFB11	0.6	TENM3	0.57	GPR176	0.548	CLEC5A	0.526	FPR3

Note: Cor, correlation coefficient.

Gene	Cor	Gene	Cor	Gene	Cor	Gene	Cor	Gene	Cor	Gene	Cor	Gene
OLFML2B	0.688	VCAN	0.639	MOB3A	0.599	CNPY4	0.57	PTMS	0.547	GSDME	0.526	TMSB10
EFEMP2	0.688	COL8A2	0.639	LRRC15	0.599	GREM1	0.569	LAMP5	0.547	EVL	0.523	ITGB5
AEBP1	0.687	ISLR	0.636	FCER1G	0.598	CEBPB	0.569	MMP9	0.546	KIF3C	0.523	CCM2
SYDE1	0.686	SPHK1	0.634	TSPAN9	0.598	LRRC8C	0.569	PLEKHO1	0.545	LOXL1	0.523	MAF
COL6A3	0.686	FSTL1	0.634	SPOCD1	0.597	HES4	0.568	MYO5A	0.544	CHSY1	0.521	SLAMF8
TNC	0.685	CLIC4	0.633	FEZ1	0.597	RFLNB	0.567	CD86	0.543	ADAM19	0.521	LIMK1
MRC2	0.685	COL10A1	0.632	UBTD1	0.596	THBS2	0.567	CDK14	0.542	NID2	0.521	ASPN
C1QTNF6	0.684	DSE	0.632	SH3PXD2B	0.596	RBMS1	0.567	RAB3IL1	0.542	AP1M1	0.521	PHLDB2
TSHZ3	0.684	PDGFRB	0.63	RGS19	0.596	CALU	0.566	TCF7L1	0.542	KATNAL1	0.519	SERPING1
ZNF469	0.683	NREP	0.63	CALD1	0.596	COL8A1	0.565	TPST1	0.541	CDH13	0.519	
Note: Cor, correlation coefficient.												

Table 3
LGALS1 negatively related genes.

Gene	Cor	Gene	Cor	Gene	Cor	Gene	Cor	Gene	Cor
SH3BGRL2	-0.675	MANSC1	-0.567	LLGL2	-0.542	BICDL2	-0.527	ALDH1A1	-0.508
RBM47	-0.647	C1orf210	-0.565	KIAA1211L	-0.542	MYH14	-0.526	SLC37A1	-0.508
ATP8B1	-0.635	PRKAB1	-0.564	CLCN3	-0.542	C1orf116	-0.525	ABHD2	-0.508
PLEKHA7	-0.624	CYP3A5	-0.564	CYP2C18	-0.541	AFDN	-0.524	RAB17	-0.507
FOXA1	-0.611	ACOX1	-0.563	ATP10B	-0.541	TST	-0.523	MYZAP	-0.507
TJP3	-0.61	MYO5B	-0.563	MUC20	-0.54	AHCYL2	-0.522	ABCD3	-0.507
LIPH	-0.607	CEACAM5	-0.561	FUT6	-0.54	PIP5K1B	-0.521	NOSTRIN	-0.506
FAM83E	-0.607	FAM3D	-0.559	OCLN	-0.539	ETFDH	-0.52	MFSD9	-0.506
TMPRSS2	-0.6	TMEM45B	-0.558	ABLIM1	-0.538	PLEKHH1	-0.518	FUT3	-0.506
SOWAHB	-0.596	UBL3	-0.554	ACADSB	-0.538	FAM221A	-0.518	PSCA	-0.506
GPD1L	-0.593	MYO5C	-0.554	ST6GALNAC1	-0.538	SSTR1	-0.518	FM05	-0.506
POF1B	-0.59	TSPAN12	-0.553	UNC13B	-0.538	ATP8A1	-0.517	SMPD3	-0.505
ERBB3	-0.588	ARFGEF3	-0.552	VSIG2	-0.537	HPGD	-0.517	ICA1	-0.505
ELF3	-0.588	SHROOM3	-0.551	TMEM125	-0.536	AKR7A3	-0.515	NBEAL2	-0.505
RALGPS1	-0.588	DOP1B	-0.549	RAB11FIP4	-0.536	HID1	-0.515	TTC39A	-0.504
PLEKHA6	-0.586	EPB41L1	-0.549	SELENBP1	-0.536	MECOM	-0.514	XK	-0.504
GOLPH3L	-0.586	LDHD	-0.549	RAB11FIP1	-0.536	VSIG10	-0.514	OVOL2	-0.504
GALNT12	-0.581	HDHD3	-0.548	COBL	-0.535	CEACAM7	-0.513	FUT2	-0.504
FAM3B	-0.577	CHP1	-0.545	TMEM238L	-0.535	SIM2	-0.513	LCOR	-0.503
CAMSAP3	-0.575	DUOX2	-0.544	PLS1	-0.534	MINDY1	-0.513	PLAC8	-0.503
CYP4F12	-0.575	SAMD5	-0.544	SMIM5	-0.531	PAQR8	-0.512	MYRF	-0.503
PRR15L	-0.575	B3GNT3	-0.544	PPFIBP2	-0.531	PLLP	-0.512	DEGS2	-0.501
MKRN20S	-0.574	CAPN5	-0.544	CPEB3	-0.53	KIAA0232	-0.511	SH3YL1	-0.501
BSPRY	-0.574	FA2H	-0.544	PPARG	-0.529	KLF3	-0.511	SLC35A3	-0.501
CGN	-0.571	C9orf152	-0.543	PIK3C2B	-0.527	SLC1A1	-0.51	HNF4G	-0.501
S100P	-0.57	FRK	-0.543	STX19	-0.527	CCDC125	-0.51		
SH2D4A	-0.57	EPB41	-0.543	SLC44A3	-0.527	MAML3	-0.51		
Note: Cor, correlation coefficient.									

GO and KEGG analysis

To further understand the potential function of LGALS1 in ESCA progression, we performed GO and KEGG on LGALS1 co-expressed genes. GO annotation found that LGALS1 co-expressed genes are mainly involved in endothelial cell differentiation, transforming growth factor receptor signaling pathway, epithelial cell proliferation, and ECM receptor interaction (Fig. 5A and online Table S1). KEGG found that LGALS1 co-expressed genes are mainly involved in leukocyte migration, transcriptional dysregulation during cancer, and PI3K/AKT signaling pathways (Fig. 5B and Table 4). GSEA showed that elevated LGALS1 was mainly enriched for ECM receptor interactions, cancer pathways, TGF BETA signaling pathways, and cytokine-to-cytokine interactions (Fig. 6 and Table 5).

Table 4
KEGG analysis of LGALS1 co-expressed genes.

ID	Description	Count	pvalue	p. adjust
hsa04974	Protein digestion and absorption	17	1.22E-10	2.84E-08
hsa04510	Focal adhesion	22	3.30E-09	3.86E-07
hsa05205	Proteoglycans in cancer	22	5.27E-09	4.11E-07
hsa04933	AGE-RAGE signaling pathway in diabetic complications	14	1.44E-07	8.43E-06
hsa04512	ECM-receptor interaction	13	2.14E-07	1.00E-05
hsa04926	Relaxin signaling pathway	14	3.38E-06	0.0001
hsa00532	Glycosaminoglycan biosynthesis-chondroitin sulfate /dermatan sulfate	6	6.28E-06	0.0002
hsa04380	Osteoclast differentiation	13	1.58E-05	0.0005
hsa04145	Phagosome	13	9.71E-05	0.0023
hsa04670	Leukocyte transendothelial migration	11	9.80E-05	0.0023
hsa05165	Human papillomavirus infection	20	0.0002	0.0040
hsa05146	Amoebiasis	10	0.0002	0.0040
hsa04611	Platelet activation	11	0.0002	0.0044
hsa04151	PI3K-Akt signaling pathway	20	0.0005	0.0080
hsa05133	Pertussis	8	0.0006	0.0087
hsa05202	Transcriptional misregulation in cancer	13	0.0007	0.0103
hsa04810	Regulation of actin cytoskeleton	14	0.0008	0.0112
hsa04540	Gap junction	8	0.0015	0.0186
hsa05130	Pathogenic Escherichia coli infection	13	0.0015	0.0186
hsa04071	Sphingolipid signaling pathway	9	0.0027	0.0320
hsa04530	Tight junction	11	0.0032	0.0352
hsa00601	Glycosphingolipid biosynthesis - lacto and neolacto series	4	0.0041	0.0439
hsa04928	Parathyroid hormone synthesis, secretion and action	8	0.0047	0.0480
hsa05152	Tuberculosis	11	0.0051	0.0497

Table 5
GSEA analysis of possible signaling pathways associated with increased LGALS1 expression.

Name	SIZE	NES	NOM p-val
KEGG_ECM_RECEPTOR_INTERACTION	84	2.157	0
KEGG_FOCAL_ADHESION	199	2.118	0
KEGG_GLYCOSAMINOGLYCAN_BIOSYNTHESIS_CHONDROITIN_SULFATE	22	1.962	0
KEGG_REGULATION_OF_ACTIN_CYTOSKELETON	212	1.850	0.004
KEGG_RENAL_CELL_CARCINOMA	70	1.791	0.004
KEGG_BLADDER_CANCER	42	1.747	0.006
KEGG_PATHWAYS_IN_CANCER	325	1.704	0.004
KEGG_DILATED_CARDIOMYOPATHY	90	1.684	0.034
KEGG_HYPERTROPHIC_CARDIOMYOPATHY_HCM	83	1.662	0.037
KEGG_PRION_DISEASES	35	1.643	0.023
KEGG_ARRHYTHMOGENIC_RIGHT_VENTRICULAR_CARDIOMYOPATHY_ARVC	74	1.593	0.044
KEGG_CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION	262	1.578	0.047
KEGG_SMALL_CELL_LUNG_CANCER	84	1.572	0.036
KEGG_TGF_BETA_SIGNALING_PATHWAY	85	1.544	0.033
KEGG_GLYCOSAMINOGLYCAN_BIOSYNTHESIS_HEPARAN_SULFATE	26	1.511	0.024
KEGG_PANCREATIC_CANCER	70	1.510	0.043
KEGG_GAP_JUNCTION	89	1.487	0.033
KEGG_GLIOMA	65	1.465	0.049
KEGG_MELANOMA	71	1.417	0.047

PPI network analysis, hub gene expression and clinical significance analysis

By identifying the functions of LGALS1 co-expressed genes, the potential biological function of LGALS1 was speculated. The PPI network relationship is shown in Fig. 7A. The hub genes are COL1A1, FN1, COL1A2, COL3A1, and COL5A1., COL5A2, COL4A2, COL18A1, COL6A2, and COL6A1 (Fig. 7B and Table 6). In the GEPIA database, we found that LGALS1 was related to hub genes in ESCA (Fig. 8). Further analysis of the expression of the hub gene in ESCA and its diagnostic value in the TCGA database. We found that COL1A1, FN1, COL1A2, COL3A1, COL5A1, COL5A2, COL4A2, COL18A1, and COL6A1 are abnormally expressed in the ESCA tissue of the TCGA database (Fig. 9) and have diagnostic significance (Fig. 10, $P < 0.05$), while the expression and diagnostic value of COL6A2 in ESCA is not statistically significant.

Table 6
Hub genes in PPI networks.

Name	description	Score
COL1A1	Collagen type I alpha 1 chain	47
FN1	Fibronectin 1	47
COL1A2	Collagen type I alpha 2 chain	44
COL3A1	Collagen type III alpha 1 chain	41
COL5A1	Collagen type V alpha 1 chain	36
COL5A2	Collagen type V alpha 2 chain	34
COL4A2	Collagen type IV alpha 2 chain	34
COL18A1	Collagen type XVIII alpha 1 chain	33
COL6A2	Collagen type VI alpha 2 chain	32
COL6A1	Collagen type VI alpha 1 chain	31

Discussion

Studies have shown that LGALS1 expression is elevated in cancer tissues such as gastric cancer, ovarian cancer, and neuroblastoma, and is associated with poor prognosis in gastric cancer, ovarian cancer, and neuroblastoma patients [11, 21–23]. However, the expression and potential clinical value of LGALS1 in

esophageal cancer tissues have not been reported in the literature. We analyzed the Oncomine, Timer, and TCGA databases and found that LGALS1 expression was elevated in ESCA tissues, which was consistent with the expression in gastric, ovarian, and neuroblastoma. Moreover, the expression level of LGALS1 was also related to age, race, weight, smoking history, cancer stage, tumor grade, histological subtype and lymph node metastasis in ESCA patients. In addition, ROC analysis found that LGALS1 had an AUC of 0.8511 in ESCA and was statistically significant. These results indicate that LGALS1 is involved in ESCA progress and is expected to become a potential new target for diagnosis and treatment of ESCA.

Currently, LGALS1 acts as an oncogene in tumors to promote cancer progression. For example, Galectin-1 is upregulated in hepatocellular carcinoma cells and can regulate hepatocellular carcinoma cell adhesion, polarization, and tumor growth in vivo [24]. Galectin-1 overexpression can activate FAK/PI3K/AKT signaling pathway to induce the resistance of EMT and sorafenib in liver cancer [25]. Galectin-1 can also cause β -catenin nuclear translocation in liver cancer, as well as increased TCF4/LEF1 transcriptional activity, cyclin D1 and proto-oncogene expression [26]. TLR (Toll-like receptor) can mediate PI3K activation regulation through Galectin-1 production, and then participate in regulating ovarian cancer cell invasion and metastasis [27]. Galectin-1 overexpression promotes the proliferation and metastasis of pancreatic cancer cells, and can promote the expression of fibronectin, collagen type I, α -SMA, MMP-2 and TIMP-1 through the TGF- β /Smad signaling pathway [28]. In gastric cancer, overexpression of Galectin-1 can enhance TGF- β signaling through positive feedback, reduce cancer cell apoptosis, and promote cancer cell migration and invasion [29]. Most cytokines are synthesized by immune cells and secrete a small class of proteins with a wide range of biological activities. Interfering with LGALS1 expression can down-regulate M2 macrophages and myeloid-derived suppressor cells (MDSCs), and suppress immunosuppressive cytokines, and immunosuppressive microenvironment of glioma [30]. Galectin-1 can inhibit the viability, proliferation, and Th1 cytokine production of non-malignant T cells in patients with leukemia skin T-cell lymphoma [31]. These results indicate that LGALS1 can participate in tumor progression through PI3K/AKT signaling pathway, TGF- β signaling pathway, and regulation of cytokines secreted by immune cells. We performed GO, KEGG, and GSEA analysis of mRNA expression data in the TCGA database. GO shows that LGALS1 co-expressed genes are mainly involved in endothelial cell differentiation, transforming growth factor receptor signaling pathway, epithelial cell proliferation, and ECM receptor interaction. LGALS1 may be involved in the progression of ESCA including leukocyte migration, transcriptional disorders during cancer, PI3K/AKT signaling pathway, ECM receptor interaction, cancer pathway, TGF BETA signaling pathway, cytokine and cytokine interaction, etc. Combined with the report, LGALS1 can participate in cancer progression through the PI3K/AKT signaling pathway, TGF- β signaling pathway, and regulate the secretion of cytokines by immune cells. We believe that LGALS1 can participate in the development of ESCA through PI3K/AKT signaling pathway, TGF BETA signaling pathway, cancer pathway, cytokine and cytokine interaction.

The hub genes in the PPI network are COL1A1, FN1, COL1A2, COL3A1, COL5A1, COL5A2, COL4A2, COL18A1, COL6A2, and COL6A1. The Hub gene has extremely important clinical significance in the progress of cancer. COL1A1 and fibronectin 1 (FN1) are highly expressed in esophageal squamous cell carcinoma (ESCC) tissues. Both COL1A1 and FN1 can promote ESCC cell proliferation and invasion [32, 33]. COL1A2 is significantly down-regulated in colorectal cancer (CRC) tissues, and COL1A2 mRNA expression levels are related to tumor differentiation, invasion, and lymph node metastasis in CRC patients. COL1A2 overexpression inhibited CRC cell line proliferation, migration, and invasion [34]. COL3A1 expression is elevated in CRC tissues and cells. The increase of COL3A1 expression is related to T stage, Dukes stage, grade, recurrence, etc. in patients with CRC. Patients with elevated COL3A1 expression had poorer overall and disease-free survival. COL3A1 in plasma has an AUC of 0.92 in CRC. Silencing COL3A1 expression can inhibit CRC cell proliferation [35]. Interfering the expression of COL5A1 in metastatic lung adenocarcinoma cells inhibits cell growth and invasion, and induces apoptosis [36]. Increased IDO1 expression promotes gastric cancer cell migration. Interfering with IDO1 expression in GC cells reduced LOXL2, COL6A1, COL6A2, and COL12A1 mRNA and protein expressions [37]. These results indicate that these hub genes are related to tumorigenesis and development.

We analyzed the correlation between LGALS1 and hub genes in the GEPIA database. In addition, we found in the TCGA database that COL1A1, FN1, COL1A2, COL3A1, COL5A1, COL5A2, COL4A2, COL18A1, and COL6A1 are elevated in ESCA tissue and have diagnostic significance. LGALS1 is involved in the progression of ESCA and is a new diagnostic target for ESCA patients. In other tumors, studies have reported that Hub genes and PI3K/AKT signaling pathways, TGF- β signaling pathways, and cytokine regulatory mechanisms have extremely important roles. The regulatory relationships between LGALS1 and Hub genes, PI3K/AKT signaling pathway, TGF- β signaling pathway, and cytokines in ESCA are unclear, and further research and verification are needed.

In summary, we show that the increased expression of LGALS1 is related to the clinicopathological characteristics of ESCA patients and can be used as a potential target for ESCA diagnosis. Moreover, LGALS1 may promote the development of ESCA through PI3K/AKT signaling pathway, TGF BETA signaling pathway, cancer pathway, cytokine and cytokine interaction.

Conclusion

LGALS1 expression is elevated in ESCA patients and may be a potential diagnostic marker for ESCA patients. PI3K/AKT signaling pathway, TGF BETA signaling pathway, cancer pathway, cytokine and cytokine interaction may be an important pathway for regulation in occurrence and development of ESCA.

Abbreviations

ESCA

Esophagus cancer; TIMER:Tumor Immune Estimation Resource; TCGA:The Cancer Genome Atlas; GO:Gene Ontology; KEGG:Kyoto Encyclopedia of Genes and Genomes; GSEA:Gene Set Enrichment Analysis; PPI:protein-protein interaction; GEPIA:Gene Expression Profiling Interactive Analysis; ROC:receiver operating characteristic; AUC:area under the curve; OS:overall survival; Gal:Galectin-1; BP:biological processes; MF:molecular functions; CC:cellular components; NES:Nominal enrichment scores;CHOL:cholangiocarcinoma; HNSC:head and neck squamous cell carcinoma; KIRC:Kidney renal clear cell carcinoma; LIHC:Liver hepatocellular carcinoma; BRCA:breast invasive carcinoma; LUAD:lung adenocarcinoma; LUSC:lung squamous cell carcinoma.

Declarations

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Not applicable.

Authors' contributions

GJL and JYM are responsible for experimental design and implementation of the scheme, LD, YH, and LY are responsible for data collection, article writing and figures editing, and GQ, GJL, and JYM are responsible for data verification and proofreading.

All authors read and approved the final manuscript.

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Conflict of Interest Statement

The authors declare no conflicts of interest.

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Figures

Figure 1

LGALS1 is abnormally expressed in cancer tissues. (A) OncoPrint database; (B) TIMER. Notes: (A) red represents increased expression of LGALS1 in cancer tissues, blue represents decreased expression of LGALS1 in cancer tissues; (B) red represents cancer tissues, blue expresses normal tissues; *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

Figure 2

Expression of LGALS1 in ESCA and its diagnostic value in the TCGA database. (A) Increased expression of LGALS1 in ESCA; (B) ROC analysis of the diagnostic value of LGALS1 in ESCA. Notes: Normal, esophageal tissue; ESCA, esophageal cancer; AUC, area under the curve.

Figure 3

LGALS1 expression level correlates with clinicopathological characteristics of ESCA patients. (A) age; (B) race; (C) weight; (D) Smoking; (E) cancer stages; (F) tumor grade; (G) tumor histology; (H) lymphatic metastasis. Notes: N, lymphatic metastasis; *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

Figure 4

LGALS1 co-expressed genes. (A) Hot map showing the top 10 co-expressed genes of LGALS1 positive and negative correlation; (B) LGALS1 co-expressed the top 3 co-expressed genes of positive correlation; (C) LGALS1 co-expressed the top 3 co-expressed genes of negative correlation. Notes: positive, positively related genes; negative, negatively related genes; Cor, correlation coefficient.

Figure 5

GO and KEGG analysis of LGALS1 co-expressed genes. (A) GO; (B) KEGG.

Figure 6

GESA analysis of related signaling pathways enriched in LGALS1 overexpression. (A) ECM receptor interaction; (B) cancer pathway; (C) TGF BETA signaling pathway; (D) cytokine-cytokine interaction.

Figure 7

LGALS1 co-expressed genes to build a protein-protein interaction network (A) PPI network; (B) Hub gene. Note: The red nodes represent positively related genes, and the blue nodes represent negatively related genes.

Figure 8

Correlation between LGALS1 and hub genes in esophageal cancer from the GEPIA database. (A) COL1A1; (B) FN1; (C) COL1A2; (D) COL3A1; (E) COL5A1; (F) COL5A2; (G) COL4A2; (H) COL18A1; (I) COL6A2; (J) COL6A1.

Figure 9

Hub gene expression in ESCA patient tissues in the TCGA database. (A) COL1A1; (B) FN1; (C) COL1A2; (D) COL3A1; (E) COL5A1; (F) COL5A2; (G) COL4A2; (H) COL18A1; (I) COL6A1. Note: Normal, normal esophageal tissue; Tumor, esophageal cancer tissue.

Figure 10

Diagnostic value of the hub gene in ESCA patients in the TCGA database. (A) COL1A1; (B) FN1; (C) COL1A2; (D) COL3A1; (E) COL5A1; (F) COL5A2; (G) COL4A2; (H) COL18A1; (I) COL6A1.