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Clinical and Translational Research

Association and prognostic significance of alpha-L-fucosidase-1 and matrix metalloproteinase 9 expression in esophageal squamous cell carcinoma

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Abstract

BACKGROUND

Alpha-L-fucosidase-1 (FUCA1) has been demonstrated to play opposing regulatory roles in adenocarcinoma and non-adenocarcinoma. Moreover, recent studies reported that FUCA1 could decrease the invasion capability by downregulating matrix metalloproteinase 9 (MMP-9) expression. However, the potential role and prognostic significance of FUCA1 in esophageal squamous cell carcinoma (ESCC) have not yet been explored.

AIM

To evaluate the status, association, and prognostic value of FUCA1 and MMP-9 expression in ESCC.

Ethics Committee at the Sun Yat-Sen University Cancer Center (No. B2014-110).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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METHODS

Patients who underwent esophagectomy for ESCC between January 1, 2014, and December 31, 2014 at Sun Yat-Sen University Cancer Center were enrolled. The expression status of FUCA1 and MMP-9 in cancerous tissues was detected using immunohistochemistry. In addition, the expression profiles of the *FUCA1* and *MMP-9* genes in non-metastatic ESCC were extracted from The Cancer Genome Atlas (TCGA) database.

RESULTS

High expression of FUCA1 and MMP-9 was found in 90 patients (75.6%) and 62 patients (52.1%), respectively. In the high FUCA1 expression group, the constituent ratios of patients with stage III disease (61.1% *vs* 37.9%, $P = 0.029$), lymphatic invasion (62.2% *vs* 31.0%, $P = 0.003$), and high MMP-9 expression (60.0% *vs* 27.6%, $P = 0.002$) were significantly higher than those in the low FUCA1 expression group. In Kaplan-Meier univariate analysis, advanced tumor-node-metastasis stage (III, $P = 0.001$), positive regional lymph node metastasis (N+, $P = 0.002$), high FUCA1 expression ($P = 0.001$), and high MMP-9 expression ($P = 0.002$) were potential predictors of shorter overall survival (OS), which was similar to the results analyzed based on the TCGA database. Further Cox multivariate regression analyses still demonstrated that FUCA1 and MMP-9 expression levels were independent prognostic factors of OS [hazard ratio (HR): 0.484, 95% confidence interval (CI): 0.239-0.979; $P = 0.044$; and HR: 0.591, 95% CI: 0.359-0.973, $P = 0.039$, respectively].

CONCLUSION

FUCA1 cooperation with MMP-9 may have a major role in affecting the ESCC invasion and metastatic capability, and serve as a valuable prognostic biomarker in ESCC.

Key Words: Esophageal squamous cell carcinoma; Alpha-L-fucosidase-1; Matrix metalloproteinase-9; Immunohistochemistry

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Core Tip: Our results demonstrated that high alpha-L-fucosidase-1 (FUCA1) expression was significantly associated with a worse overall survival, which illustrated that FUCA1 may have the ability to promote tumor cell invasion and metastasis among patients with esophageal squamous cell carcinoma (ESCC). Moreover, this study provides additional evidence that the molecular mechanisms of FUCA1 in ESCC are entirely different.

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INTRODUCTION

Esophageal squamous cell carcinoma (ESCC) is the predominantly diagnosed histological subtype in China, accounting for approximately 90% of all esophageal carcinomas (EC)[1]. Although more advances in early screening and multimodal therapy have been approved for use in patients with ESCC, the long-term survival rates even after curative surgery remain unsatisfactory[2-4]. This undesirable prognosis appears to be triggered mostly by aggressive tumor cell invasion and metastasis. Novel modalities for ESCC treatment that target molecular pathways are required to change the prognostic dilemma[5]. In addition, patients diagnosed with

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ESCC of the same stage show varied prognoses[2,3]. Hence, it is also necessary to explore the potential molecular mechanisms of ESCC as prognostic factors to distinguish those patients with a high-risk of local recurrence and/or distant metastasis[2].

The alpha-L-fucosidase-1 (*FUCA1*) gene, targeted by the *p53* tumor suppression gene, encodes a lysosomal enzyme named *FUCA1*[6]. Its main biological function in human cells is to degrade alpha-L-fucose-containing glycoproteins and glycolipids to inhibit cell growth and induce cell death[5-7]. Moreover, a recent study elaborated that *FUCA1* could inhibit the activation and fucosylation of epidermal growth factor receptor (EGFR), thereby blocking the EGFR signaling pathway[6]. Therefore, in theory, the molecular function of *FUCA1* appears to diminish the invasion capacity of tumor cells (Figure 1). The association of high *FUCA1* expression in serum or tumor tissue with a favorable prognosis in triple-negative breast cancer and intrahepatic cholangiocarcinoma has been confirmed[8,9]. However, probably due to molecular mechanistic heterogeneity, some studies have reported that elevated *FUCA1* content predicts worse survival outcomes in hepatocellular carcinoma and glioma[7,10]. To our knowledge, it is unknown whether *FUCA1* is expressed in ESCC and whether the expression status of *FUCA1* is related to the prognostic outcome of ESCC.

The matrix metalloproteinase (MMP) family, consisting of a group of zinc-containing enzymes that can degrade the extracellular matrix and destroy the basement membrane, plays a critical role in epithelial and mesenchymal tumor invasion and metastasis (Figure 1)[11,12]. Many previous studies and meta-analyses have proven that overexpression of MMP family proteins in ESCC is associated with an unfavorable survival[11-13]. Notably, further studies discovered that *FUCA1* could downregulate MMP-9 expression and activity, thereby diminishing the invasive ability of intrahepatic cholangiocarcinoma and breast cancer[9,14]. However, no relationship between *FUCA1* expression and MMP-9 expression in ESCC has been reported.

Therefore, the main aim of this study was to evaluate the prognostic significance of *FUCA1* and MMP-9 expression in ESCC and investigate the correlation of *FUCA1* expression with MMP-9 expression.

MATERIALS AND METHODS

The Cancer Genome Atlas data acquisition

The gene expression profiles in tumor tissues, clinical information, survival times, and outcomes of patients diagnosed with ESCC without distant metastasis were obtained from the public The Cancer Genome Atlas (TCGA) database (<https://tcga-data.nci.nih.gov/tcga/>). The skewed data of *FUCA1* and MMP-9 expression profiles were log-transformed to reduce skewness. Then, on the basis of the best cutoff value determined by using X-tile 3.6.3 software (Copyright Yale University 2003), the log-transformed gene expression levels were divided into two groups (high/low).

Patient selection

The clinical, pathological, and follow-up information of all patients who underwent curative esophagectomy for EC from January 1, 2014 to December 31, 2014 at the Sun Yat-Sen University Cancer Center (SYSUCC) was retrospectively collected from the Hospital Information System. All tumor-node-metastasis (TNM) staging was reclassified according to the 8th edition of the American Joint Committee on Cancer Staging Manual. Subsequently, only patients who met the following criteria were retained: (1) Diagnosed with thoracic ESCC; (2) Underwent complete removal (R0); (3) No induction therapy; (4) No death occurred within 30 d after operation; (5) No other primary neoplasm; (6) Had adequate paraffin-embedded specimens for immunohistochemical staining; and (7) Had complete follow-up information. A total of 119 consecutive patients were enrolled in this study (Figure 2).

Written informed consent was obtained from all patients themselves during preoperative conversations. This retrospective study was approved by the Research Ethics Committee at the Sun Yat-Sen University Cancer Center (No. 308-2015-012).

Immunohistochemical staining and interpretation

Detection of *FUCA1* and MMP-9 in ESCC tissues was carried out by immunohistochemistry (IHC), as described in related studies[6,8]. Specifically, the paraffin slices were incubated with a rabbit anti-human *FUCA1* polyclonal antibody (dilution, 1:400; Abcam, Cambridge, United Kingdom) and a rabbit anti-human MMP-9 monoclonal antibody (dilution, 1:300; D603H, Cell Signaling Technology, Danvers, MA, United

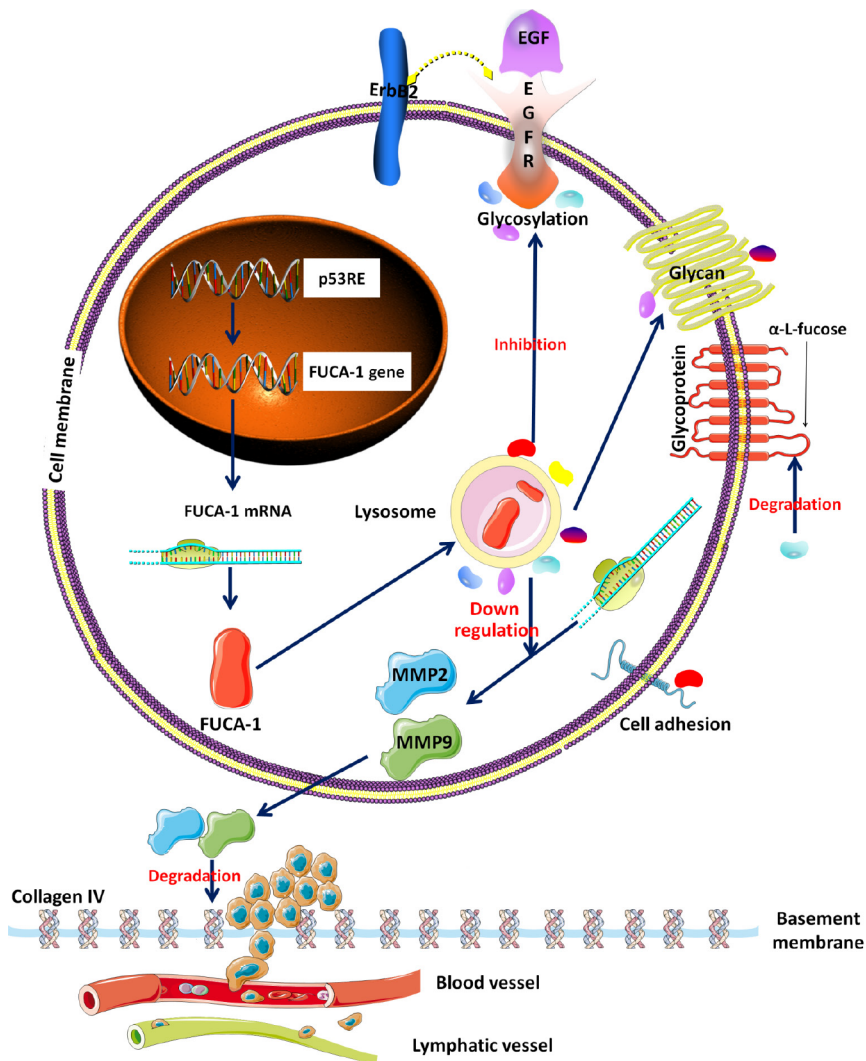


Figure 1 Schematic diagram of the regulatory mechanisms involved in the effects of alpha-L-fucosidase-1 on malignant tumor invasion and metastasis. MMP: Matrix metalloproteinase; FUCA-1: Alpha-L-fucosidase-1; EGFR: Epidermal growth factor receptor.

States). The expression of FUCA1 and MMP-9 was independently evaluated by two pathologists (Zhang MQ and Huang WT) who all engaged in pathological diagnosis over 5 years. If there was inconsistent interpretation, reevaluation under a double-head microscope was performed to obtain a consistently reliable result.

The staining intensity was graded on a four-step scale: Negative, weak, moderate, and strong, scored as 0, 1, 2, and 3, respectively. The percentage of the chromogenic reaction, counted in five random fields per section using 100 × magnification, was grouped into < 25%, 25%-50%, 50%-75%, and ≥ 75% (scored 1, 2, 3, and 4, respectively). The case was interpreted as high expression of FUCA1 and MMP-9 if moderate to strong cytoplasmic staining was observed in ≥ 25% of ESCC cells with reference to previous studies[13,15]. In addition, the total immunoreaction score was calculated according to the staining intensity (scores 0-3) multiplied by the percentage of stained ESCC cells (scores 1-4) to generate a total score from 0 to 12[13,15].

Statistical analysis

All statistical analyses were performed using SPSS 24.0 software (IBM, Chicago, IL, United States), and a two-sided *P* value less than 0.05 was defined as a statistically significant difference. Student's *t* test and χ^2 test were used to compare the differences in continuous variables and categorical variables, respectively, between the high expression group and the low expression group. Overall survival (OS) months were counted from the date of ESCC diagnosis to the date of death or the last follow-up (December 31, 2020). The Kaplan-Meier method was applied to identify the potential prognostic variables using the log-rank test. Subsequently, all of the above statistically significant variables were retained in the Cox proportional hazards model. In addition,

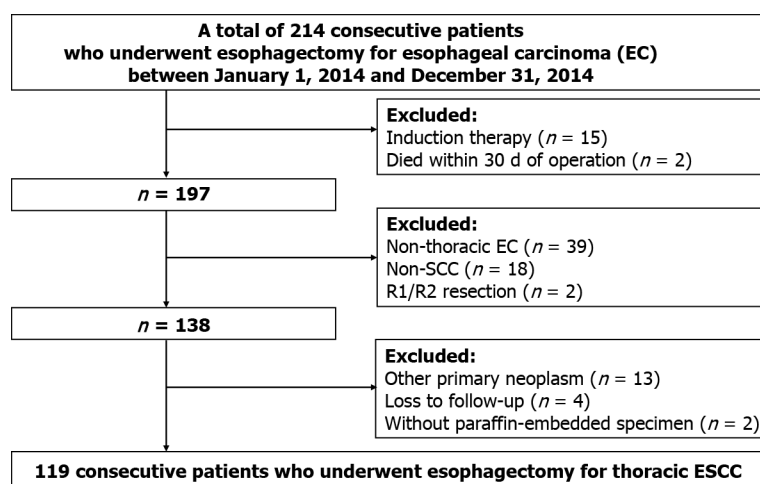


Figure 2 The inclusion and exclusion criteria for screening 119 patients from Sun Yat-Sen University Cancer Center who underwent esophagectomy for esophageal squamous cell carcinoma. EC: Esophageal carcinoma; ESCC: Esophageal squamous cell carcinoma; SCC: Squamous cell carcinoma.

scatter plots and survival curves were drawn using GraphPad Prism 8.0 software (San Diego, CA, United States).

RESULTS

Patient characteristics

Of the 119 patients from the SYSUCC, 21 (17.6%) were women, and the mean (standard deviation, SD) age of all patients was 59.0 (8.9) years. The majority of patients were smokers at the time of diagnosis (80, 67.2%) and had a history of alcohol use (74, 62.2%). The middle third of the thoracic esophagus was the most common site of ESCC (69, 58.0%), followed by the lower third (36, 30.3%). Upon pathological examination of resected specimens, the majority of tumors were limited to location between the mucosa and adventitia (pT1, 6.7%; pT2, 16.8%; pT3, 52.1%) under the microscope and had regional lymph node metastasis (pN1, 35.3%; pN2, 10.9%; pN3, 8.4%). The constituent ratios of pathological TNM stages I, II, and III were 5.0%, 39.5%, and 55.5%, respectively. In addition, 67.2% of all patients (80/119) received post-operative adjuvant chemotherapy. Among these 80 patients, 69 (86.3%) received a docetaxel plus nedaplatin/carboplatin regimen, and the remaining 11 were given a paclitaxel plus nedaplatin/carboplatin regimen.

Association of FUCA1 and MMP-9 expression with clinicopathological features

The clinicopathologic features of patients from the SYSUCC and TCGA databases according to the expression status of FUCA1 and MMP-9 are summarized in [Table 1](#) and [Supplementary Table 1](#), respectively. High expression of FUCA1 and MMP-9 in ESCC tumor cells was observed in 90 (75.6%, with a median total score of 6) and 62 patients (52.1%, with a median total score of 3), respectively. The IHC staining for FUCA1 and MMP-9 is shown in [Figure 3](#). High FUCA1 expression was more frequent in patients with positive regional lymph node metastasis ($P = 0.003$, [Figure 4A](#)) and advanced stage tumors ($P = 0.029$). In the high MMP-9 expression group, patients showed a lower proportion of smoking history (56.5% *vs* 78.9%, $P = 0.009$) and alcohol use (53.2% *vs* 71.9%, $P = 0.036$). The FUCA1 expression status and total score were positively related to the MMP-9 expression status ($P = 0.002$) and total score ($r = 0.258$, $P = 0.005$, [Figure 4B](#)), respectively. However, in TCGA data analysis, we only found that male patients ($P = 0.035$) and patients without lymph node metastasis ($P = 0.050$) had a relatively higher proportion of low MMP-9 gene expression ([Supplementary Table 1](#)).

Survival outcomes and prognostic analysis

In the SYSUCC cohort, the median OS time was 32.2 mo (range, 1-73 mo) and the 5-year OS rate was 39.5%. In univariate survival analysis, no regional lymph node metastasis (N0, $P = 0.002$), earlier TNM stage (I-II, $P = 0.001$), low FUCA1 expression (P

Table 1 Association of alpha-L-fucosidase-1 and matrix metalloproteinase 9 expression with clinicopathological characteristics in patients with resected esophageal squamous cell carcinoma from Sun Yat-Sen University Cancer Center

Variable	FUCA1 expression			MMP-9 expression		
	Low expression (n = 29)	High expression (n = 90)	P value	Low expression (n = 57)	High expression (n = 62)	P value
Age (yr, mean \pm SD)	61.2 \pm 7.6	58.3 \pm 9.2	0.137	59.5 \pm 8.4	58.6 \pm 9.4	0.587
Female, n (%)	3 (10.3)	18 (20.0)	0.236	6 (10.5)	15 (24.2)	0.058
History of smoking, n (%)	6 (20.7)	33 (36.7)	0.111	45 (78.9)	35 (56.5)	0.009 ^a
History of alcohol use, n (%)	10 (34.5)	35 (38.9)	0.670	41 (71.9)	33 (53.2)	0.036
Localization, n (%)						
Upper	2 (6.9)	12 (13.3)	0.360	5 (8.8)	9 (14.5)	0.555
Middle	20 (69.0)	49 (54.4)		33 (57.9)	36 (58.1)	
Lower	7 (24.1)	29 (32.2)		19 (33.3)	17 (27.4)	
Grade, n (%)						
Well	4 (13.8)	19 (21.1)	0.648	12 (21.1)	11 (17.7)	0.820
Moderately	16 (55.2)	48 (53.3)		31 (54.4)	33 (53.2)	
Poorly	9 (31.0)	23 (25.6)		14 (24.6)	18 (29.0)	
T stage, n (%)						
T1-2	6 (20.7)	22 (24.4)	0.678	12 (21.1)	16 (25.8)	0.541
T3-4a	23 (79.3)	68 (75.6)		45 (78.9)	46 (74.2)	
Lymphatic invasion, n (%)						
Negative (N0)	20 (69.0)	34 (47.8)	0.003 ^a	31 (54.4)	23 (37.1)	0.067
Positive (N+)	9 (31.0)	56 (62.2)		26 (45.6)	39 (62.9)	
TNM stage, n (%)						
I-II	18 (62.1)	35 (38.9)	0.029 ^a	29 (50.9)	24 (38.7)	0.182
III	11 (37.9)	55 (61.1)		28 (49.1)	38 (61.3)	
Postoperative complication, n (%)						
Arrhythmia	5 (17.2)	22 (24.4)	0.421	16 (28.1)	11 (17.7)	0.179
Pneumonia	1 (3.4)	11 (12.2)	0.172	5 (8.8)	7 (11.3)	0.649
Anastomotic leak	0 (0)	11 (12.2)	0.048 ^a	4 (7.0)	7 (11.3)	0.421
Adjuvant therapy, n (%)	19 (65.5)	61 (67.8)	0.822	36 (63.2)	44 (71.0)	0.365
FUCA1 total score (mean \pm SD)	-	-	-	4.3 \pm 3.8	7.3 \pm 4.1	0.000 ^a
High FUCA1 expression, n (%)	-	-	-	36 (63.2)	54 (87.1)	0.002 ^a
MMP-9 total score (mean \pm SD)	3.6 \pm 2.7	2.3 \pm 2.6	0.029 ^a	-	-	-
High MMP-9 expression, n (%)	8 (27.6)	54 (60.0)	0.002 ^a	-	-	-

^aP < 0.05.

FUCA1: Alpha-L-fucosidase-1; MMP-9: Matrix metalloproteinase-9; SD: Standard deviation.

= 0.001), and low MMP-9 expression ($P = 0.002$) were significantly associated with a favorable OS (Table 2). After further adjustment in the Cox proportional hazards model, the above four variables still had strong prognostic value for OS (Table 2 and Figure 5).

Table 2 Kaplan-Meier analysis and Cox multivariate regression analyses of overall survival in patients with resected esophageal squamous cell carcinoma from Sun Yat-Sen University Cancer Center

Variable	No.	Univariate analysis		Multivariate analysis	
		5-yr overall survival rate (%)	P value	Hazard ratio (95% confidence interval)	P value
Age (yr)					
< 60	61	44.3	0.133		
≥ 60	58	34.5			
Sex					
Female	21	28.6	0.510		
Male	98	41.8			
History of smoking					
Yes	39	42.5	0.533		
No	80	33.3			
History of alcohol use					
Yes	74	40.5	0.831		
No	45	37.8			
Localization					
Upper	14	21.4	0.426		
Middle	69	42.0			
Lower	36	41.7			
Grade					
Well	23	43.5	0.222		
Moderately	64	43.8			
Poorly	32	28.1			
T stage					
T1-2	28	39.3	0.890		
T3-4a	91	39.6			
Lymphatic invasion					
Negative (N0)	54	55.6	0.002 ^a	0.584 (0.351-0.972)	0.039 ^a
Positive (N+)	65	23.5		Reference	
TNM stage					
I-II	53	54.7	0.001 ^a	0.520 (0.316-0.856)	0.010 ^a
III	66	27.3		Reference	
Arrhythmia					
Yes	27	29.6	0.210		
No	92	42.4			
Pneumonia					
Yes	12	33.3	0.110		
No	107	40.2			
Anastomotic leak					
Yes	11	36.4	0.295		
No	108	39.8			

Adjuvant therapy					
Yes	80	33.7	0.159		
No	39	51.3			
FUCA1 expression					
Low	29	65.5	0.001 ^a	0.484 (0.239-0.979)	0.044 ^a
High	90	31.1		Reference	
MMP-9 expression					
Low	57	56.1	0.002 ^a	0.591 (0.359-0.973)	0.039 ^a
High	62	24.2		Reference	

^a*P* < 0.05.

FUCA1: Alpha-L-fucosidase-1; MMP-9: Matrix metalloproteinase-9.

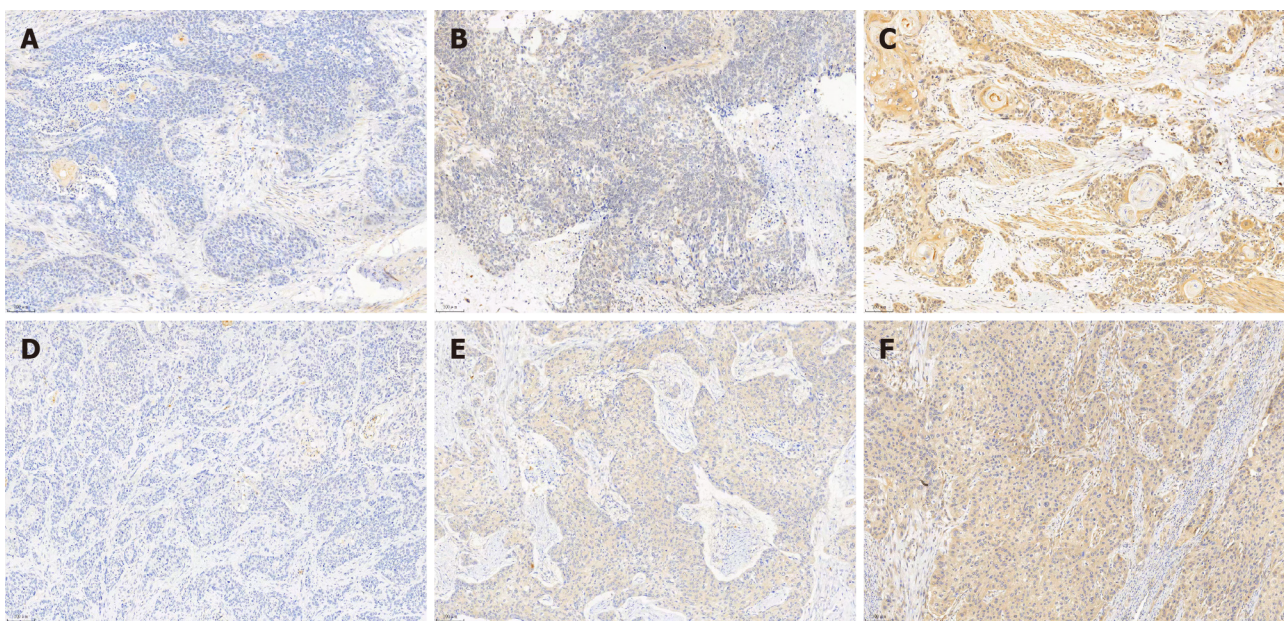


Figure 3 Immunohistochemical staining for alpha-L-fucosidase-1 and matrix metalloproteinase 9 in esophageal squamous cell carcinoma. A: Stage IA esophageal squamous cell carcinoma (ESCC) with negative expression of alpha-L-fucosidase-1 (FUCA1) (total score, 0); B: Stage IIB ESCC with low expression of FUCA1 (total score, 2); C: Stage IIB ESCC with high expression of FUCA1 (total score, 12); D: Stage IB ESCC with negative expression of matrix metalloproteinase 9 (MMP-9) (total score, 0); E: Stage IB ESCC with low expression of MMP-9 (total score, 3); F: Stage IIIA ESCC with high expression of MMP-9 (total score, 12). Original magnification: 100 ×; scale bar: 100 μm.

Similarly, after univariate and multivariate analyses, we found that nonmetastatic ESCC patients (I-III) with low *FUCA1* gene expression in the TCGA database were also significantly related to a better OS (*P* = 0.006; [Supplementary Table 2](#) and [Figure 6A](#)). However, the relationship of low MMP-9 expression with favorable prognosis was observed as a trend but with no statistical significance (*P* = 0.080; [Supplementary Table 2](#) and [Figure 6B](#)).

DISCUSSION

In this study, we detected FUCA1 protein overexpression in most ESCC tissues by IHC for the first time and found that high FUCA1 expression was positively associated with high MMP-9 expression, regional lymph node metastasis (pN+), and advanced TNM stage (III). Additionally, multivariable survival analysis showed that the FUCA1 and MMP-9 expression status could independently predict the postoperative survival of patients with resected ESCC.

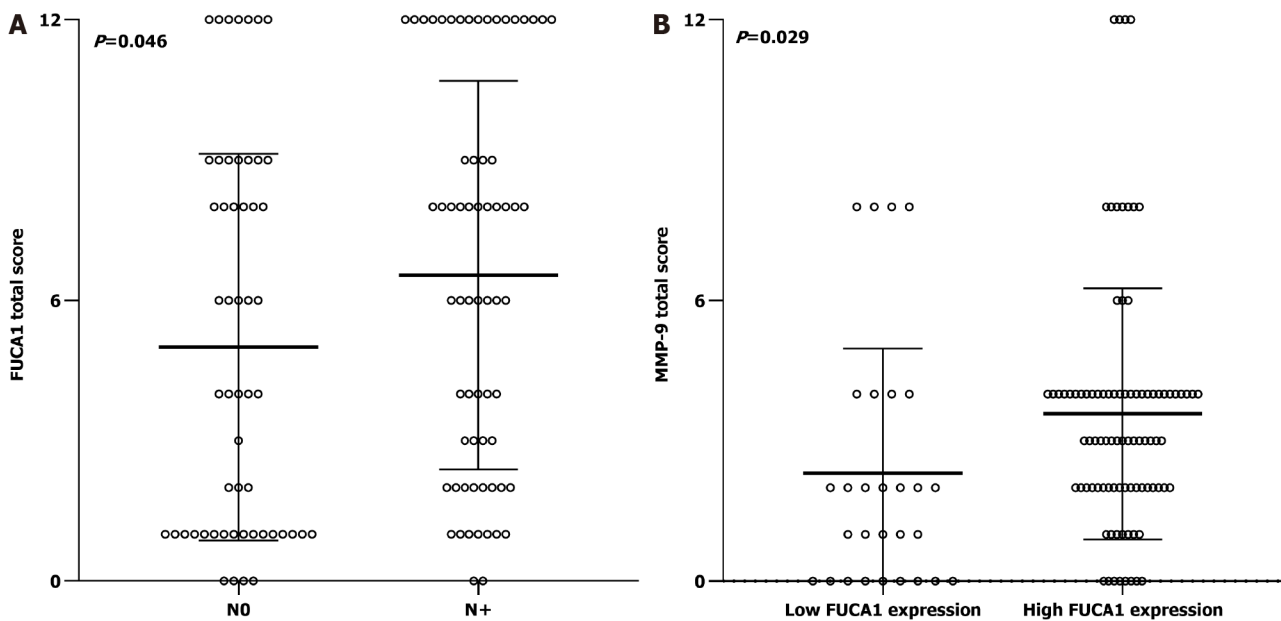


Figure 4 Correlation analysis. A: Positive lymph node metastasis (N+) is associated with a high alpha-L-fucosidase-1 (FUCA1) total score; B: Low FUCA1 expression is associated with a low matrix metalloproteinase 9 total score. FUCA1: Alpha-L-fucosidase-1.

In 2015, Tzu-Chun Cheng and his colleagues reported that upregulation of FUCA1 expression in triple-negative breast cancer (adenocarcinoma) conferred a favorable OS by degrading cell surface glycoproteins and glycolipids to inhibit cell growth and induce cell death[8]. Subsequently, the association of higher FUCA expression (≥ 20.85 U/L) with a better prognosis in patients with intrahepatic cholangiocarcinoma (adenocarcinoma) was also confirmed. Further mechanistic investigations revealed that FUCA could diminish the invasive ability of tumor cells by downregulating MMP-9 expression[9]. In addition, another recent study on thyroid cancer demonstrated that FUCA1 expression was higher in normal thyroids and papillary thyroid carcinomas than in poorly differentiated, metastatic, and anaplastic thyroid carcinoma; in other words, lower FUCA1 expression was related to a worse prognosis of thyroid cancer (adenocarcinoma)[15]. Similarly, Otero-Estévez *et al*[16] reported that the expression and activity of FUCA1 in colorectal cancer (adenocarcinoma) showed a gradual decrease from early to advanced stage, and patients with a low FUCA1 level were significantly associated with a higher tumoral recurrence rate. However, there were controversial reports concerning the relationship between FUCA1 expression and prognostic survival in non-adenocarcinoma malignancies (*i.e.*, hepatocellular carcinoma, glioma, and ESCC)[5,7,10,17]. Two early studies reported that a high preoperative serum FUCA level ($> 35/\mu\text{L}$) was significantly associated with a worse recurrence-free survival and OS in patients with hepatocellular carcinoma following hepatectomy[7,17]. Recently, another study also found that FUCA overexpression had a negative effect on the prognosis of glioma[10]. The prognostic roles of FUCA1 overexpression in hepatocellular carcinoma and glioma were in agreement with our findings in ESCC. Through further mechanistic studies, they elaborated the following novel mechanisms. First, the lack of FUCA1 protein could promote the development of numerous acidic vacuoles that participate in the autophagic cell death process. Second, FUCA1 overexpression induced tumor-associated macrophage recruitment by upregulating chemokines 2/5 expression, but this pathway could be inhibited by introducing *FUCA1* silenced RNA[10]. Moreover, correlation analyses showed that FUCA1 overexpression was associated with higher proportions of local invasion, higher pathological grade, and lymphatic metastasis[7,10,17]. The above evidence from mechanistic studies and retrospective cohort studies all illustrated that FUCA1 may have the ability to promote tumor cell invasion and metastasis among patients with non-adenocarcinoma[7,10,17]. Therefore, FUCA1 may be used not only as a prognostic biomarker but also as a novel therapeutic target for hepatocellular carcinoma, glioma, and ESCC. In addition, on the basis of the above studies, it became apparent that the molecular mechanisms of FUCA1 were quite different in adenocarcinoma and non-adenocarcinoma malignancies, and further studies are warranted to elucidate the potential molecular pathways in ESCC.

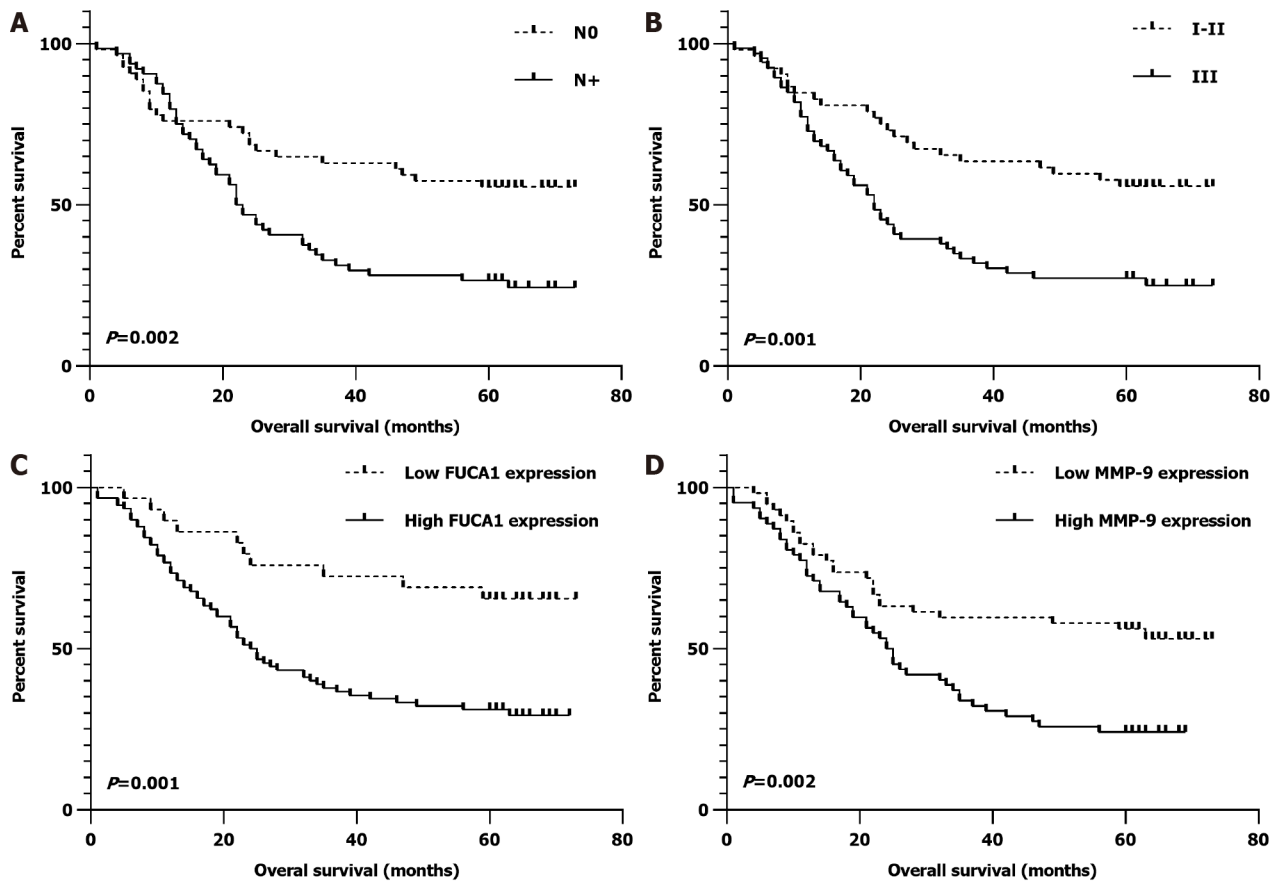


Figure 5 Kaplan-Meier curves of overall survival in the Sun Yat-Sen University Cancer Center cohort. A: Lymphatic invasion (N0/N+); B: Pathological tumor-node-metastasis stage (I-II/III); C: Alpha-L-fucosidase-1 expression (low/high); D: Matrix metalloproteinase 9 expression (low/high). MMP-9: Matrix metalloproteinase 9; FUCA-1: Alpha-L-fucosidase-1.

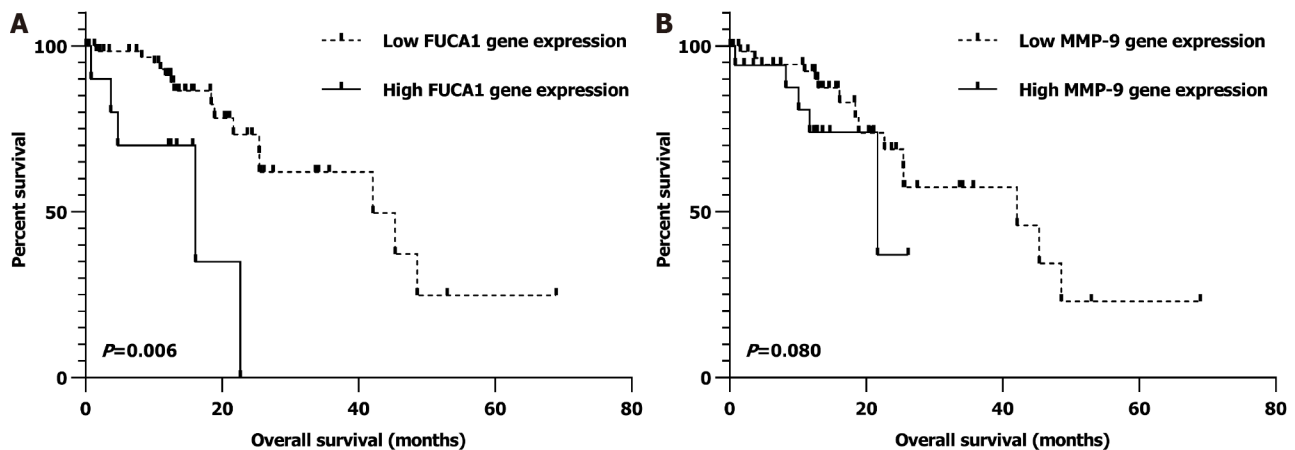


Figure 6 Kaplan-Meier curves of overall survival in The Cancer Genome Atlas database. A: Alpha-L-fucosidase-1 expression (low/high); B: Matrix metalloproteinase 9 expression (low/high). MMP-9: Matrix metalloproteinase 9; FUCA-1: Alpha-L-fucosidase-1.

Many studies observed MMP-9 overexpression detected by IHC staining in ESCC (34.8%-90.0%), and the related mechanistic studies elaborated that MMP-9 could participate in the development and progression of ESCC mainly by degrading type IV collagen to promote tumor cell metastasis and resulted in poor prognosis, which was completely consistent with our present study[11]. However, few studies have focused on the association between FUCA1 and MMP-9 expression. Shuang *et al*[9] reported that AFU (another abbreviation form for FUCA1) significantly downregulated the expression of MMP-9 in intrahepatic cholangiocarcinoma (adenocarcinoma) *in vitro*. Another cytological experiment carried out by Yuan *et al*[14] also demonstrated that AFU could significantly reduce MMP-9 activity and expression in human breast cancer

cell lines (adenocarcinoma). Conversely, our study found that FUCA1 staining was positively associated with MMP-9 staining in ESCC, which was first reported in squamous cell carcinoma. The detailed molecular mechanisms need to be explored in the future to obtain more effective therapeutic targets in ESCC.

Although our present study clarified the prognostic significance of FUCA1 expression and the correlation of FUCA1 and MMP-9 expression in ESCC for the first time, several limitations cannot be ignored when extrapolating these results. First, this retrospective study was carried out in a single-center, small sample size cohort, which inevitably caused selection bias. Moreover, external validation in other patient cohorts was also lacking. Second, due to intratumoral heterogeneity, the paraffin section used for IHC staining may not represent the entire tumor mass. To obtain the most representative staining, all paraffin slices used in this study included ESCC tissues and corresponding normal esophageal tissues without necrotic tissue. Third, the antibodies selected in this study were not completely the same as those used in previous studies [12,13,15,18]. Undeniably, different antibodies may vary the IHC staining results. Fourth, the consensus cutoff values for FUCA1 and MMP-9 staining interpretation had not been determined; thus, there may be variation in the statistical results in which different cutoff values were used. In this study, the threshold value was selected for interpreting high and low FUCA1/MMP-9 expression with reference to previous large cohort studies [12,13,15,18].

CONCLUSION

FUCA1 cooperation with MMP-9 may have a major role in affecting the ESCC invasion and metastatic capability and serve as a valuable prognostic biomarker in ESCC.

ARTICLE HIGHLIGHTS

Research background

Fundamental studies discovered that alpha-L-fucosidase-1 (FUCA1) could down-regulate matrix metalloproteinase 9 (MMP-9) expression and activity, thereby diminishing the invasive ability of intrahepatic cholangiocarcinoma and triple-negative breast cancer; thus, high FUCA1 expression and low MMP-9 expression in serum or tumor tissue are associated with a favorable prognosis. However, likely due to molecular mechanistic heterogeneity, some studies have reported that elevated FUCA1 content predicts worse survival outcomes in hepatocellular carcinoma and glioma.

Research motivation

To explore the prognostic significance of FUCA1 and MMP-9 expression in esophageal squamous cell carcinoma (ESCC) and investigate the correlation of FUCA1 expression with MMP-9 expression.

Research objectives

A total of 119 consecutive patients who underwent esophagectomy for ESCC between January 1, 2014 and December 31, 2014 at the Sun Yat-Sen University Cancer Center (SYSUCC) were enrolled in the final analysis. In addition, the *FUCA1* and *MMP-9* gene expression profiles of 76 patients diagnosed with ESCC without distant metastasis were obtained from the public The Cancer Genome Atlas (TCGA) database.

Research methods

Student's *t* test and χ^2 test were used to compare the differences in continuous variables and categorical variables, respectively. The Kaplan-Meier method was applied to identify the potential prognostic variables using the log-rank test. Subsequently, all of the above statistically significant variables were retained in the Cox proportional hazards model.

Research results

In the SYSUCC cohort, the FUCA1 expression status (high/low) and total IHC score were positively related to the MMP-9 expression status (high/low, $P = 0.002$) and total IHC score ($r = 0.258$, $P = 0.005$). Moreover, after further adjusting in the Cox propor-

tional hazards model, low FUCA1 expression ($P = 0.001$) and low MMP-9 expression ($P = 0.002$) still showed significant associations with a favorable overall survival (OS). Similarly, after univariate and multivariate analysis, we found that nonmetastatic ESCC patients (I-III) with low *FUCA1* gene expression in the TCGA database also had a significantly better OS ($P = 0.006$). However, the relationship of low MMP-9 expression with a favorable prognosis was observed as a trend but with no statistical significance ($P = 0.080$).

Research conclusions

FUCA1 cooperation with MMP-9 may have a major role in affecting ESCC invasion and metastasis capability and serve as a valuable prognostic biomarker in ESCC.

Research perspectives

The present study offers a future research direction in which FUCA1 cooperation with MMP-9 may be a potential regulator in ESCC progression, which needs to be explored in fundamental studies.

REFERENCES

- 1 Yang S, Lin S, Li N, Deng Y, Wang M, Xiang D, Xiang G, Wang S, Ye X, Zheng Y, Yao J, Zhai Z, Wu Y, Hu J, Kang H, Dai Z. Burden, trends, and risk factors of esophageal cancer in China from 1990 to 2017: an up-to-date overview and comparison with those in Japan and South Korea. *J Hematol Oncol* 2020; **13**: 146 [PMID: 33138852 DOI: 10.1186/s13045-020-00981-4]
- 2 Yu X, Gao S, Xue Q, Tan F, Gao Y, Mao Y, Wang D, Zhao J, Li Y, He J, Mu J. Development of a predictive nomogram for cause-specific mortality in surgically resected early-stage oesophageal cancer: a Surveillance, Epidemiology, and End Results (SEER) analysis. *J Thorac Dis* 2020; **12**: 2583-2594 [PMID: 32642166 DOI: 10.21037/jtd.2020.03.25]
- 3 Yu X, Wen Y, Lin Y, Zhang X, Chen Y, Wang W, Wang G, Zhang L. The value of preoperative Glasgow Prognostic Score and the C-Reactive Protein to Albumin Ratio as prognostic factors for long-term survival in pathological T1N0 esophageal squamous cell carcinoma. *J Cancer* 2018; **9**: 807-815 [PMID: 29581759 DOI: 10.7150/jca.22755]
- 4 Kakeji Y, Oshikiri T, Takiguchi G, Kanaji S, Matsuda T, Nakamura T, Suzuki S. Multimodality approaches to control esophageal cancer: development of chemoradiotherapy, chemotherapy, and immunotherapy. *Esophagus* 2021; **18**: 25-32 [PMID: 32964312 DOI: 10.1007/s10388-020-00782-1]
- 5 Yu X, Zhang R, Yang T, Zhang M, Xi K, Lin Y, Wen Y, Wang G, Huang Z, Zhang X, Zhang L. Alpha-L-fucosidase: a novel serum biomarker to predict prognosis in early stage esophageal squamous cell carcinoma. *J Thorac Dis* 2019; **11**: 3980-3990 [PMID: 31656672 DOI: 10.21037/jtd.2019.08.92]
- 6 Ezawa I, Sawai Y, Kawase T, Okabe A, Tsutsumi S, Ichikawa H, Kobayashi Y, Tashiro F, Namiki H, Kondo T, Semba K, Aburatani H, Taya Y, Nakagama H, Ohki R. Novel p53 target gene FUCA1 encodes a fucosidase and regulates growth and survival of cancer cells. *Cancer Sci* 2016; **107**: 734-745 [PMID: 26998741 DOI: 10.1111/cas.12933]
- 7 Wang K, Guo W, Li N, Shi J, Zhang C, Lau WY, Wu M, Cheng S. Alpha-L-fucosidase as a prognostic indicator for hepatocellular carcinoma following hepatectomy: a large-scale, long-term study. *Br J Cancer* 2014; **110**: 1811-1819 [PMID: 24569461 DOI: 10.1038/bjc.2014.102]
- 8 Cheng TC, Tu SH, Chen LC, Chen MY, Chen WY, Lin YK, Ho CT, Lin SY, Wu CH, Ho YS. Down-regulation of α -L-fucosidase 1 expression confers inferior survival for triple-negative breast cancer patients by modulating the glycosylation status of the tumor cell surface. *Oncotarget* 2015; **6**: 21283-21300 [PMID: 26204487 DOI: 10.18632/oncotarget.4238]
- 9 Shuang Z, Mao Y, Lin G, Wang J, Huang X, Chen J, Duan F, Li S. Alpha-L-Fucosidase Serves as a Prognostic Indicator for Intrahepatic Cholangiocarcinoma and Inhibits Its Invasion Capacity. *Biomed Res Int* 2018; **2018**: 8182575 [PMID: 29682557 DOI: 10.1155/2018/8182575]
- 10 Xu L, Li Z, Song S, Chen Q, Mo L, Wang C, Fan W, Yan Y, Tong X, Yan H. Downregulation of α -L-fucosidase 1 suppresses glioma progression by enhancing autophagy and inhibiting macrophage infiltration. *Cancer Sci* 2020; **111**: 2284-2296 [PMID: 32314457 DOI: 10.1111/cas.14427]
- 11 Zeng R, Duan L, Kong Y, Liang Y, Wu X, Wei X, Yang K. Clinicopathological and prognostic role of MMP-9 in esophageal squamous cell carcinoma: a meta-analysis. *Chin J Cancer Res* 2013; **25**: 637-645 [PMID: 24385690 DOI: 10.3978/j.issn.1000-9604.2013.11.03]
- 12 Li Y, Ma J, Guo Q, Duan F, Tang F, Zheng P, Zhao Z, Lu G. Overexpression of MMP-2 and MMP-9 in esophageal squamous cell carcinoma. *Dis Esophagus* 2009; **22**: 664-667 [PMID: 19191857 DOI: 10.1111/j.1442-2050.2008.00928.x]
- 13 Xia T, Tong S, Fan K, Zhai W, Fang B, Wang SH, Wang JJ. XBP1 induces MMP-9 expression to promote proliferation and invasion in human esophageal squamous cell carcinoma. *Am J Cancer Res* 2016; **6**: 2031-2040 [PMID: 27725908]
- 14 Yuan K, Listinsky CM, Singh RK, Listinsky JJ, Siegal GP. Cell surface associated alpha-L-fucose moieties modulate human breast cancer neoplastic progression. *Pathol Oncol Res* 2008; **14**: 145-156 [PMID: 18553163 DOI: 10.1007/s12253-008-9036-x]

- 15 **Vecchio G**, Parascandolo A, Allocca C, Ugolini C, Basolo F, Moracci M, Strazzulli A, Cobucci-Ponzano B, Laukkanen MO, Castellone MD, Tsuchida N. Human α -L-fucosidase-1 attenuates the invasive properties of thyroid cancer. *Oncotarget* 2017; **8**: 27075-27092 [PMID: [28404918](#) DOI: [10.18632/oncotarget.15635](#)]
- 16 **Otero-Estévez O**, Martínez-Fernández M, Vázquez-Iglesias L, Páez de la Cadena M, Rodríguez-Berrocal FJ, Martínez-Zorzano VS. Decreased expression of alpha-L-fucosidase gene FUCA1 in human colorectal tumors. *Int J Mol Sci* 2013; **14**: 16986-16998 [PMID: [23965968](#) DOI: [10.3390/ijms140816986](#)]
- 17 **Zhou Y**, Ma X, Wu J, Zhang C, Wang B, Song B, Guo W, Pan B. Preoperative serum α -1-fucosidase as an early-recurrent indicator for hepatocellular carcinoma following curative resection. *Zhonghua Yi Xue Za Zhi* 2014; **94**: 3623-3628 [PMID: [25622951](#)]
- 18 **Ishida S**, Kayamori K, Sakamoto K, Yukimori A, Kugimoto T, Harada H, Ikeda T. Alpha-L-fucosidase-1 is a diagnostic marker that distinguishes mucoepidermoid carcinoma from squamous cell carcinoma. *Pathol Int* 2019; **69**: 76-85 [PMID: [30729618](#) DOI: [10.1111/pin.12764](#)]



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