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Expression and prognostic significance of MAGE-A11 and transcription factors (SP1,TFCP2 and ZEB1) in ESCC tissues

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ABSTRACT

Objective: To evaluate the clinical characteristics and prognostic significance of MAGE-A11 and transcription factors (SP1, TFCP2 and ZEB1) in patients with esophageal squamous cell carcinoma (ESCC).
Methods: To assess the expression of MAGE-A11 and transcription factors (SP1, TFCP2 and ZEB1) in 121 ESCC samples were respectively detected by immunohistochemical method.
Results: The results showed MAGE-A11 and transcription factors (SP1,TFCP2 and ZEB1) expression were associated with some clinical features in patients, such as pathological differentiation, tumor size, clinical stage, lymph node metastasis and distant metastasis. Kaplan-Meier analysis showed that patients with ESCC having high MAGE-A11 and transcription factors (SP1,TFCP2 and ZEB1) expression had a worse prognosis compared to the patients with low expression. Multivariate Cox proportional hazards regression model revealed that MAGE-A11 expression, TFCP2 expression, lymph node metastasis and distant metastasis were independently associated with ESCC patients' survival.
Conclusions: High expression of MAGE-A11 and transcription factors (SP1,TFCP2 and ZEB1) in ESCC tissues suggests promoting ESCC progression and poor prognosis, co-expression of MAGE-A11 and transcription factors even worse.

1. Introduction

Esophageal squamous cell carcinoma (ESCC) is one of the most common human malignant tumors, its mortality rate situated the seventh in all tumor disease worldwide [1]. However, due to economic and dietary habits, ESCC is the forth leading cancer in incidence in China [2]. Cancer early detection can improve the survival of patients with ESCC, but the prognosis remains poor [3]. Therefore, it is particularly important to find reliable prognostic indicators.

MAGE-A11 was first identified as a protein interacting with androgen receptor(AR) in human testicular tissue and highly expressed in a variety of human body tumor tissues [4–7]. Transcription factor specificity protein 1 (SP1) is one of sequence specific DNA binding proteins, and abnormally expressed in several human tumors [8]. In recent years, it has been realized that SP1 is closely associated with proliferation, invasion, migration and angiogenesis of tumor cells [9,10]. Transcriptional factor CP2 (TFCP2), also known as LBP-1c and LSF, involved in many biological processes, including cell cycle, cell growth and development [11,12]. Transcription factor zinc finger E-box binding homeobox 1 (ZEB1) contains 2 zin. finger clusters and 1 homologous domains. Recent studies indicate that ZEB1 is involved in the occurrence and development of a variety of tumors [13,14]. We have discovered that transcription factors SP1, TFCP2 and ZEB1 directly bind to MAGE-A11 promoter [5]. However, their prognostic significance of patients with ESCC is unclear up to now.

In this study, we detected MAGE-A11 and transcription factors (SP1,TFCP2 and ZEB1) proteins expression in tumor tissues of patients with ESCC by using immunohistochemical technique and analyzed their correlation with clinicopathological risk factors and prognosis. We attempted to identify the possibility of MAGE-A11 and transcription factors (SP1, TFCP2 and ZEB1) as ESCC biological markers for prognostic evaluation.

2. Materials and methods

2.1. Patients and specimens

Surgical primary ESCC tissues and corresponding adjacent normal

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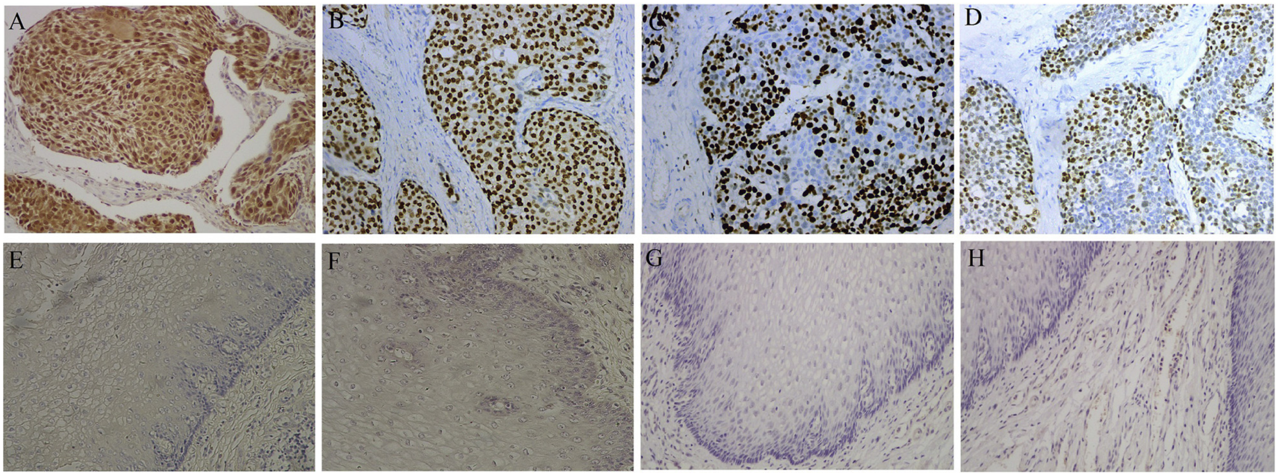

Fig. 1. The section showed the IHC staining of MAGE-A11 and transcription factors (SP1, TFCP2 and ZEB1) in ESCC and adjacent normal tissues. Expression of MAGE-A11 in ESCC and adjacent normal tissues. (A) Positive expression of MAGE-A11 in ESCC specimens, × 20, (E) Negative expression of MAGE-A11 in adjacent normal tissues, × 20. Expression of SP1 in ESCC and adjacent normal tissues. (B) Positive expression of SP1 in ESCC specimens, × 20, (F) Negative expression of SP1 in adjacent normal tissues, × 20. Expression of TFCP2 in ESCC and adjacent normal tissues. (C) Positive expression of TFCP2 in ESCC specimens, × 20, (G) Negative expression of TFCP2 in adjacent normal tissues, × 20. Expression of ZEB1 in ESCC and adjacent normal tissues. (D) Positive expression of ZEB1 in ESCC specimens, × 20, (H) Negative expression of ZEB1 in adjacent normal tissues, × 20.

tissues were obtained from 121 ESCC cases, which were all in patients for surgical treatment in the Fourth Affiliated Hospital, Hebei Medical University from February 2013 to October 2013. All of the tissues were embedded in paraffin for large-scale immunohistochemical (IHC) analysis. All study subjects were ethnically homogeneous Han nationality and residents of Hebei Province and its surrounding regions and informed consent was obtained from all recruited cases. One (or more) first- or second-degree relatives with esophageal/cardia/gastric cancer were defined as having family history of upper gastrointestinal cancers (UGIC). Information on clinicopathologic characteristics was available from hospital recordings and pathological diagnosis. The study was approved by the Ethics Committee of the Fourth Affiliated Hospital, Hebei Medical University.

2.2. IHC staining and evaluation

4 μm of paraffin-embedded tissue sections were deparaffinized in xylene, andrehydrated through graded alcohol. The sections were then washed with phosphate buffered saline (PBS, pH 7.2) for 3 × 5 min. Then, these sections were heated in a microwave oven for 5 min in 10 mmol/L Na-citric buffer (pH 6.0) for antigen retrieval and washed with PBS. The sections were immersed in 0.3% hydrogen peroxide in methanol for 20 min to suppress endogenous peroxidase activity. After washed with PBS, the sections were incubated in 1:10 diluted normal goat serum at room temperature in a humidified chamber for 45 min to prevent nonspecific immunoglobulin binding. The sections were then treated with rabbit anti-MAGE-A11 polyclonal antibody (1:500) (Abcam, USA), rabbit anti-SP1 polyclonal antibody (1:200) (Santa Cruz, USA), mouse anti-TFCP2 monoclonal antibody (1:200) (BD Biosciences, USA) or rabbit anti-ZEB1 monoclonal antibody (1:100) (Abcam, USA) at 4∘C over night. Normal IgG replaced of the primary antibody served as the control. A streptoavidin-biotinylated horseradish peroxidase-based detection system was used to reveal specific binding. Sections were counterstained with hematoxylin for light microscopic review and evaluation. The expression of MAGE-A11 was detected in both cytoplasm and nucleus of cells. SP1, TFCP2 and ZEB1 mainly located in the nucleus. The expression was analyzed by the intensity of positive cells using Image J soft-ware and was ranked on the sum of intensity and area from 0 to 7: 0–2, negative expression; 3–7, positive staining (of those, 3–4, weak positive expression; and 5–7, strong positive expression). Staining intensity was graded as follows: 0 for no staining; 1 for mild staining; 2 for moderate staining; and 3 for intense staining. We multiply the two together and the product < 4 is negative expression, ≥ 4 is positive expression.

2.3. Statistical analysis

Statistical analysis was performed with SPSS22.0 software (SPSS lnc, Chicago, IL, USA). The potential association between MAGE-A11 or transcription factors (SP1, TFCP2 and ZEB1) expression and clinicopathological risk factors was analyzed with Chi-square or Fisher's exact test, as appropriate. Survival curves were made by using the Kaplan-Meier method and the Log-rank or the Breslow tests were used as needed for the univariate comparison of MAGE-A11 or transcription factors (SP1, TFCP2 and ZEB1) expression categories. The Cox proportional hazards model was used for multivariate analysis to examine the potential prognostic value of different variables on overall survival. All statistical tests were two sided and $P < 0.05$ was considered statistically significant.

3. Results

3.1. High expression of MAGE-A11 and transcription factors (SP1, TFCP2 and ZEB1) proteins in tumor tissues of patients with ESCC

MAGE-A11 and transcription factors (SP1, TFCP2 and ZEB1) protein levels were measured in 121 ESCC tissues and corresponding adjacent normal tissues. The results of IHC showed that MAGE-A11 was expressed in both the cytoplasm and the nucleus of ESCC tissues (Fig. 1A). Transcription factors (SP1, TFCP2 and ZEB1) were expressed in the nucleus of ESCC tissues (Fig. 1B, C, D). Our study showed that MAGE-A11 did not expressed in the normal esophageal epithelial tissues, but expressed in 57.85% of ESCC tissues (Fig. 1A, Table 1). We also found that the positive expression of SP1, TFCP2 and ZEB1 were 12.40%, 9.10% and 16.53% in normal esophageal epithelial tissues, and that of SP1, TFCP2 and ZEB1 separately were 47.11%, 39.67% and 56.20% in ESCC. (Fig. 1B, C, D, Table 1). The expression of MAGE-A11 and transcription factors (SP1, TFCP2 and ZEB1) proteins were positive in tumor tissues of case 1 patient; the expression of MAGE-A11 protein was positive and transcription factors (SP1, TFCP2 and ZEB1) proteins were negative in tumor tissues of case 2 patient; the expression of MAGE-A11 protein was negative and transcription factors (SP1, TFCP2

Table 1
Methylation status and expression of MAGE-A11 in ESCC tumor tissues and corresponding normal tissues.

Group	N	MAGE-A11		Sp1		TFCP2		ZEB1	
		n(%)	*P*	n(%)	*P*	n(%)	*P*	n(%)	*P*
Tumor tissues	121	70(57.85)	< 0.01	57(47.11)	< 0.01	48(39.67)	< 0.01	68(56.20)	< 0.01
Normal tissues	121	0(0)		15(12.40)		11(9.10)		20(16.53)	

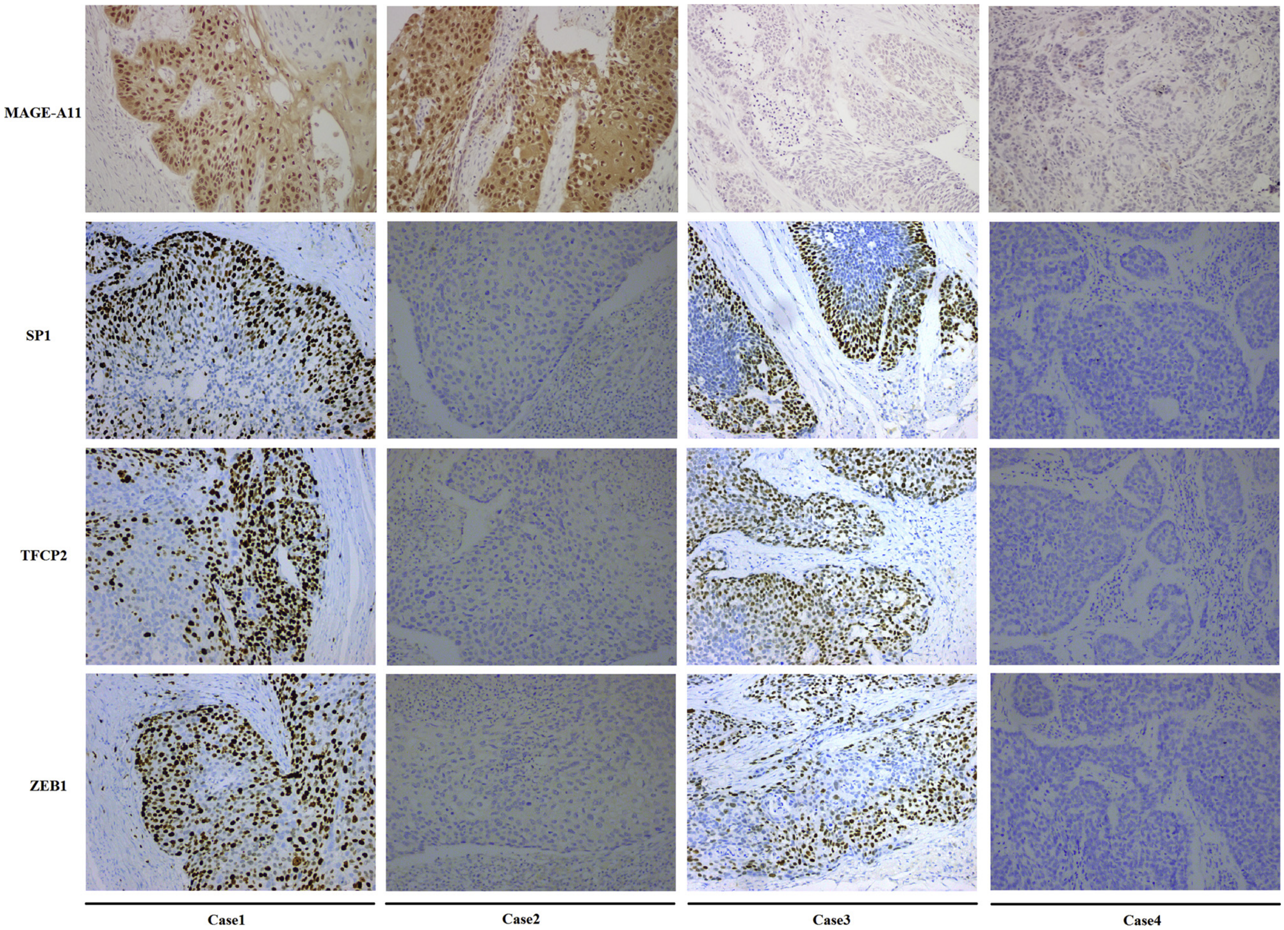

Fig. 2. The representative tumor tissue samples with expression of MAGE-A11 and transcription factors (SP1, TFCP2 and ZEB1) in ESCC patients. Case 1: MAGE-A11 (+)/ SP1 (+)/ TFCP2 (+)/ ZEB1 (+); Case 2: MAGE-A11(+)/ SP1 (-)/ TFCP2 (-)/ ZEB1(-); Case 3: MAGE-A11 (-)/ SP1 (+)/ TFCP2 (+)/ ZEB1 (+); Case 4: MAGE-A11 (-)/ SP1 (-)/ TFCP2 (-)/ ZEB1 (-).

and ZEB1) proteins were positive in tumor tissues of case 3 patient; the expression of MAGE-A11 and transcription factors (SP1, TFCP2 and ZEB1) proteins were negative in tumor tissues of case 4 patient (Fig. 2).

3.2. Different correlations between MAGE-A11 and transcription factors (SP1, TFCP2 and ZEB1) proteins expression and the clinicopathpological factors of patients with ESCC

For further exploring the possible effect of MAGE-A11 and transcription factors (SP1, TFCP2 and ZEB1) proteins in ESCC, we evaluated the correlation between MAGE-A11 and transcription factors (SP1, TFCP2 and ZEB1) proteins expression and the clinicopathological factors of ESCC patients. As shown in Table 2, MAGE-A11 expression was not correlated with the patients' age, gender and family history of UGIG ($P > 0.05$).

Elevated expression of MAGE-A11 in ESCC tissues was significantly correlated with lower histological differentiation ($P < 0.01$), worse clinical stage ($P < 0.01$), larger tumor size ($P < 0.01$), lymph node metastasis ($P < 0.01$) and distant metastasis ($P < 0.01$). High expression of SP1 in ESCC tissues was associated with worse clinical stage ($P < 0.01$), larger tumor size ($P < 0.01$), lymph node metastasis ($P < 0.01$) and distant metastasis ($P < 0.01$). High expression of TFCP2 in ESCC tissues related to lymph node metastasis ($P < 0.01$) and distant metastasis ($P < 0.01$). High expression of ZEB1 in ESCC tissues was significantly correlated with worse clinical stage ($P < 0.01$), larger tumor size ($P = 0.021$), lymph node metastasis ($P < 0.01$) and distant metastasis ($P < 0.01$). These data suggested that high expression of MAGE-A11 and transcription factors (SP1, TFCP2 and ZEB1) proteins may indicate a poor prognosis of ESCC patients.

3.3. MAGE-A11 and transcription factors (SP1, TFCP2 and ZEB1) are associated with poor prognosis of ESCC

To estimate the relationship between MAGE-A11 expression and patient survival or transcription factors (SP1, TFCP2 and ZEB1) expression and patient survival, we performed Kaplan-Meier curve analyses for overall survival. Kaplan-Meier analysis had shown that high MAGE-A11 expression preferred poor 5-year overall survival (29.41%

Table 2
Expression of MAGE-A11, SP1, TFCP2 and ZEB1 in ESCC tissues.

Clinicopathological factors	N	MAGE-A11 expression		χ^2	*P*	SP1 expression		χ^2	*P*	TFCP2 expression		χ^2	*P*	ZEB1 expression		χ^2	*P*
		low	high			low	high			low	high			low	high		
Gender				0.122	0.726			1.472	0.225			2.942	0.086			0.013	0.909
Men	93	40	53			52	41			60	33			41	52		
Woman	28	11	17			12	16			13	15			12	16		
Age/year				0.787	0.375			0.256	0.613			0.083	0.773			0.624	0.429
< 50	41	15	26			23	18			24	17			20	21		
≥50	80	36	44			41	39			49	31			33	47		
Family history of UGIC				0.705	0.401			0.945	0.331			1.335	0.248			0.547	0.459
No	73	33	40			36	37			41	32			30	43		
Yes	48	18	30			28	20			32	16			23	25		
Pathological differentiation				15.786	< 0. 01			2.587	0.108			0.594	0.441			1.090	0.296
Well/moderate	83	45	38			48	35			52	31			39	44		
Poor	38	6	32			16	22			21	17			14	24		
Clinical stage				20.547	< 0.01			7.426	< 0.01			0.348	0.555			9.466	< 0.01
I–II	54	35	19			36	18			31	23			32	22		
III-IV	67	16	51			28	39			42	25			21	46		
Tumor size(cm)				23.945	< 0. 01			7.940	< 0.01			0.668	0.414			5.298	0.021
≤5	61	39	22			40	21			39	22			33	28		
> 5	60	12	48			24	36			34	26			20	40		
Lymph node metastasis				41.791	< 0.01			30.954	< 0.01			11.844	< 0.01			20.046	< 0.01
N_0	27	26	1			27	0			24	3			22	5		
N_+	94	25	69			37	57			49	45			31	63		
Distant metastasis				40.528	< 0.01			25.033	< 0.01			20.555	< 0.01			27.381	< 0.01
M_0	61	43	18			46	15			49	12			41	20		
M_+	60	8	52			18	42			24	36			12	48		

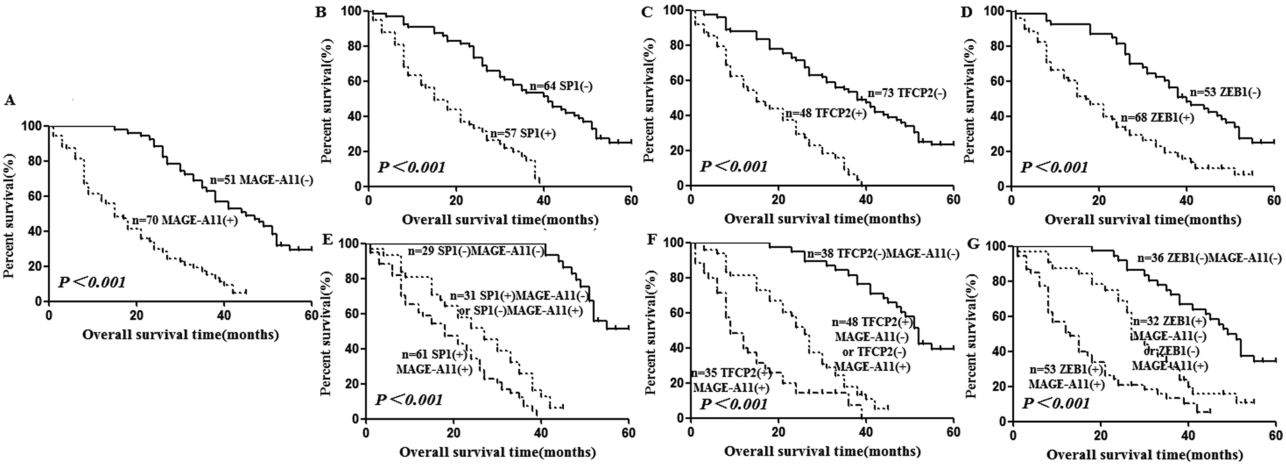

Fig. 3. Kaplan-Meier survival analysis of MAGE-A11 and transcription factors (SP1, TFCP2 and ZEB1) expression in ESCC cases. (A) Showing a direct correlation between high MAGE-A11 expression and poor patient survival. (B) Showing consistently a direct correlation between high SP1 expression and poor patient survival. (C) Showing consistently a direct correlation between high TFCP2 expression and poor patient survival. (D) Showing consistently a direct correlation between high ZEB1 expression and poor patient survival. (E) ESCC cases with high expression of MAGE-A11 and SP1 showing poor survival. (F) ESCC cases with high expression of MAGE-A11 and TFCP2 showing poor survival. (G) ESCC cases with high expression of MAGE-A11 and ZEB1 showing poor survival.

vs. 10.00%). The median overall survival of high MAGE-A11 expression patients was 21 months, and the median overall survival of MAGE-A11 low expression patients was 45 months (Fig. 3A). Patients with high expression level of transcription factors (SP1, TFCP2 and ZEB1) usually had a shorter survival time and worse prognosis than those with low transcription factors (SP1, TFCP2 and ZEB1) expression level (Fig. 3B, C and D). Moreover, co-expression of MAGE-A11 and transcription factors (SP1, TFCP2 and ZEB1) predicted unfavorable prognosis (Fig. 3E, F and G).

To further investigate prognostic factors for poor ESCC outcome, univariate and multivariate analyses were performed. In univariate analysis, overall survival was correlated significantly with MAGE-A11 expression, SP1 expression, TFCP2 expression, ZEB1 expression, clinical stage, lymph node metastasis, as well as distant metastasis (Table 2). Clinical stage includes tumor size, lymph node metastasis and distant metastasis. Excluding their interactions, just lymph node metastasis and distant metastasis entered the regression model.

Multivariate analysis revealed that high expression of MAGE-A11, high expression of TFCP2, lymph node metastasis and distant metastasis were independent prognostic factors in ESCC patients (Table 3).

4. Discussion

Gene expression requires strict regulation and gene activation or

Table 3
Univariate and multivariate analyses of prognostic factors in ESCC for overall survival.

Variable	Univariate analysis			Multivariate analysis		
	HR	*P* value	95% CI	HR	*P* value	95% CI
MAGE-A11 expression High vs Low	4.496	< 0.01	2.763–7.317	1.989	0.026	1.085–3.646
SP1 expression High vs Low	3.344	< 0.01	2.135–5.237	1.281	0.333	0.776–2.114
TFCP2 expression High vs Low	3.507	< 0.01	2.256–5.453	1.974	0.005	1.229–3.172
ZEB1 expression High vs Low	2.969	< 0.01	1.940–4.544	1.335	0.248	0.818–2.180
Gender Male vs Female	1.371	0.173	0.870–2.160			
Age(years) < 50 vs ≥50	0.720	0.112	0.480–1.080			
Family history of UGIC Yes vs No	1.335	0.154	0.898–1.986			
Pathological differentiation Well/moderate vs Poor	1.340	0.182	0.872–2.061			
Tumor size(cm) ≤5 vs > 5	1.560	0.031	1.041–2.337	1.189	0.481	0.735–1.922
Clinical stage I and II vs III and IV	2.618	< 0.01	1.721–3.985			
Metastatic state of lymph node Yes vs No	6.273	< 0.01	3.391–11.606	2.804	0.013	1.239–6.350
Distant metastasis Yes vs No	25.661	< 0.01	11.883–55.418	15.370	< 0.01	6.768–34.901

suppression play an important role in expression. Gene expression program of cells is regulated by epigenetic regulation mechanism and the activities of sequence-specific transcription factors. Transcription factors bind to specific regulatory sequences in DNA and regulate the transcription by promoting the recruitment of transcription initiation mechanisms. Transcription factors affect the biological action of cells, including cell proliferation, apoptosis and differentiation, and have a significant role in the process of growth and development [15]. In recent years, transcription factors are closely related to the occurrence and development of tumors [16]. Therefore we can target transcription factors to cure tumor by modulating their expression or degradation.

MAGE-A11 is unique among the MAGE-A family which is involved in the regulation of transcriptional activity of androgen-dependent androgen receptor (AR). MAGE-A11 can directly interact with Skp2 and Cyclin A, and regulate the substrate specificity of Skp2-mediated protein degradation [17]. Our previous research has been reported that MAGE-A11 expression is a predictive marker of poor prognosis in breast cancer, laryngeal squamous cell carcinoma and glioma, and promotes the growth of tumor cells, as well as proliferation and invasiveness [6,7,18]. SP1 was sequence specificity and identified as a transcriptional activator of the major early Simian Virus 40 (SV40) promoter by using HeLa cells [19]. According to a study, Sp1 is related to the regulation of tissue-specific, cell cycle, and signaling pathway response genes [20]. SP1 plays an important role in many human diseases including cancer. Recent studies have demonstrated that TFCP2 has an oncogenic role in various malignant disorders, including hepatocellular carcinoma [21], colorectal cancer [22] and melanoma [23]. The ZEB1 transcription factor is now known as a inducer of invasiveness and EMT. Previous research found that ZEB1 can regulate the expression of many genes in a variety of tumor cells and is closely associated with the genesis and development of cancer and the invasion and metastasis of tumor cells [24,25]. Previous studies in our laboratory expressed that transcription factor TFCP2 and ZEB1 can directly bind to the promoter of MAGE-A11 and regulate the expression of MAGE-A11 in a methylation-dependent manner in ESCC cells. SP1 can directly bind at the MAGE-A11 promoter in prostate cancer cells, contribute to MAGE-A11 promoter activity and endogenous gene expression [26]. However, prognostic significance of transcription factors (SP1, TFCP2 and ZEB1) and whether MAGE-A11 is influenced by them in ESCC are not clear.

In this study, we found that MAGE-A11 and transcription factors (SP1, TFCP2 and ZEB1) proteins all had different degree expressions in ESCC tissues. There was a significant correlation between MAGE-A11 level and tumor histological grades. The positive rate of MAGE-A11 was higher in low differentiation ESCC tissues than that in high differentiation ESCC tissues. These results suggest that MAGE-A11 may be involved in the differentiation of tumor cells. At the same time, there were interrelation of different degree between MAGE-A11 and transcription factors (SP1, TFCP2 and ZEB1) and clinical stage, larger tumor size, lymph node metastasis and distant metastasis. The pathological indexes mentioned above were closely associated with prognosis of the disease. The result was similar to those that have been documented. SP1 was correlated with tumor stage and a poor prognosis [20]. High expression of TFCP2 in colorectal cancer was significantly correlated with large tumor size, advanced AJCC stage and high Ki-67 index [12]. Expression of ZEB1 in cervical squamous cell carcinoma cells was positively associated with vascular invasion and lymph node metastasis [27].

We further calculated the survival rate with the Kaplan Meier method, compared the survival curves in Log-rank test and analyzed the prognostic factors with Cox regression. ESCC patients with positive expression of MAGE-A11 had significantly reduced 5-year overall survival. A multivariate Cox regression analysis showed that MAGE-A11 and TFCP2 expression are independent poor prognostic factors of ESCC. SP1 and ZEB1 were not independent risk factors in patients with ESCC. Which can be assumed, a possible interaction between TFCP2 and SP1 or ZEB1 should be considered. This hypothesis needs further experiments to confirm. Moreover, co-expression of MAGE-A11 and transcription factors (SP1, TFCP2 and ZEB1) predicted more poorly prognosis. This result further evidenced that transcription factors (SP1, TFCP2 and ZEB1) contribute to MAGE-A11 promoter activity and endogenous gene expression. Our results indicated that transcription factors (SP1, TFCP2 and ZEB1) may up-regulate of MAGE-A11 gene transcriptional activity, contribute to gene expression, promote the occurrence and development of ESCC and affect the prognosis. Thus, we might consider the combination of antigen peptide targeting MAGE-A11 and transcription factor inhibitors to cure ESCC. However, the compensatory phenomena among different transcription factors must be considered in the development of transcription-specific transcription factor inhibitors.

5. Conclusion

To sum up, the study reveals that the expression of MAGE-A11 and transcription factors (SP1, TFCP2 and ZEB1) are closely related to the occurrence and development, lymph node metastasis and distant metastasis. They can be used as comprehensive indexes to assist clinical evaluation of prognosis.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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