European Review for Medical and Pharmacological Sciences 2018; 22: 422-429

LncRNA CASC9 promotes tumorigenesis by affecting EMT and predicts poor prognosis in esophageal squamous cell cancer

G.-D. GAO[1], X.-Y. LIU[2], Y. LIN[3], H.-F. LIU[1], G.-J. ZHANG[1]

[1]Department of Thoracic Surgery, Jining No. 1 People's Hospital, Jining, Shandong, China
[2]Department of Gastroenterology, Jining No. 1 People's Hospital, Jining, Shandong, China
[3]Department of Thoracic Surgery, Heze Municiple Hospital, Heze, Shandong, China

Guo-Dong Gao and Xiang-Yu Liu contributed equally to this work

Abstract. – OBJECTIVE: The purpose of this study was to explore the clinical significance and biological function of long noncoding RNA CASC9 (CASC9) in esophageal squamous cell carcinoma (ESCC).

PATIENTS AND METHODS: Quantitative Real-time PCR (qRT-PCR) was used to determine the expression of CASC9 in ESCC tissues and cell lines. Receiver operating characteristic curves were used to evaluate the sensitivity and specificity of CASC9. The correlation between the CASC9 levels and the clinicopathological factors of the patients was also analyzed. Then, the survival was assessed by the Kaplan-Meier method and proportional hazards model. The effects of CASC9 on ESCC cells were evaluated by Cell Counting Kit-8 (CCK-8), migration and invasion. Finally, several EMT markers expression was detected by Western blot.

RESULTS: We found that CASC9 was significantly upregulated in ESCC cell lines and clinical tissues. The CASC9 levels discriminated ESCC tissues from normal tissues with an area under the ROC curve (AUC) of 0.813. In addition, there is statistical significance between CASC9 expression level and tumor stage, lymph nodes metastasis, and clinical stage. Kaplan-Meier analysis indicated that high CASC9 expression had a significant impact on overall survival (*p* = 0.014) and disease-free survival (*p* = 0.0025). Moreover, CASC9 expression was an independent prognostic marker of overall survival and disease-free survival in a multivariate analysis. *In vitro* assay indicated that inhibition of CASC9 could suppress proliferation, migration, and invasion in ESCC. Further mechanistic studies found that aberrant CASC9 expression could modulate the expression levels of markers of EMT.

CONCLUSIONS: Our data highlight the pivotal role of CASC9 as a novel diagnostic, prognostic biomarker and a potential therapeutic target of ESCC.

Key Words:
Long noncoding RNA, CASC9, ESCC, Prognosis, Proliferation, Metastasis.

Introduction

Esophageal cancer is among the ten most incident and fatal malignancies in the world[1]. More than 90% of esophageal cancers are esophageal squamous cell carcinoma (ESCC)[2]. The incidence and mortality rate of ESCC are very high in the world, especially in China[3]. Although treatment and perioperative management have evolved in recent years, patients with local advanced or metastatic disease remain extremely poor outcome[4,5]. Furthermore, the absence of an accurate prognosis biomarker makes it difficult to analyze the survival time of ESCC patients after surgery[6]. Thus, it is an urgent necessity to identify new prognostic biomarkers or specific therapeutic targets for ESCC.

Long noncoding RNAs (lncRNAs) are a class of noncoding RNAs that are greater than 200 nucleotides in length[7]. As we all know, lncRNAs may serve as master gene regulators capable of controlling protein-coding and noncoding genes[8]. Recent studies have confirmed that lncRNAs are involved in various cellular processes, including carcinogenesis, angiogenesis, and metastasis[9,10]. In ESCC, many lncRNAs have been found to suppress proliferation and metastasis, as well as help predict the prognosis of ESCC patients[11-13]. Several researches showed that abnormal expression of lncRNAs could be used as biomarkers for the detection of ESCC[14,15]. Those results indicated that lncRNAs could exert tremendous effect in diagnosis, prognosis and treatment of this disease.

Corresponding Author: Yongjun Rui, MD; e-mail: wxswkryj@163.com

LncRNA Cancer Susceptibility Candidate 9 (CASC9) is located at 8q21.11. Previous studies indicated that abnormal CASC9 expression was found in ESCC, nasopharyngeal carcinoma and gastric cancer[16-18]. Although functional assay showed that CASC9 contributed to the development and progression of ESCC, its clinical significance and potential mechanism in ESCC remains unclear. Our present work aimed to explore the diagnostic and prognostic value of CASC9 in ESCC patients. Then, we found that CASC9 promoted ESCC proliferation and metastasis by regulation of epithelial mesenchymal transition (EMT) in ESCC.

Patients and Methods

Patients and Specimens

Surgical tumor specimens and adjacent tissue samples were obtained from 128 patients. Among the 128 patients enrolled in the present study, 77 were male and 51 were female, with an average age of 53.4 years (Table I). All tissues were histopathologically confirmed by two experienced pathologists. None of the patients received radiotherapy or chemotherapy before surgery. Tumor tissues and adjacent normal tissues were collected and stored at -80°C until use. Our present study was approved by the Medical Ethics Committee of Jining No. 1 People's Hospital. Written informed consents were signed by all participators in advance. The clinicopathological features of the ESCC patients are described in detail in Table I.

Cell Lines and Transfection

The human ESCC cell lines (KYSE30, KYSE150, TE-1, Eca-109) were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA). Human normal esophageal epithelial cells (HEEpiC) were obtained from ScienCell (Carlsbad, CA, USA). Cells were maintained in Dulbecco's modified Eagle's Medium (DMEM, Gibco, Beijing, China) supplemented with 10% fetal bovine serum (FBS), 100 U/ml penicillin and 100 μg/ml streptomycin.

Small interference RNA (siRNA) for the inhibition of CASC9 expression and negative control siRNA(si-NC) were constructed by GenePharma (Pudong, Shanghai, China). For RNA transfection, the cells were seeded into each well of 96-well plate and incubated overnight. Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA) was used for the transfection.

Real-time Quantitative PCR

Total RNA was isolated from cells and tissue specimens using TRIzol reagent (Invitrogen, Carlsbad, CA, USA). Reverse transcription of RNA was performed using the First-Strand cDNA Synthesis Kit (TaKaRa, Dalian, China). qRT-PCR analyses were performed using a standard protocol from Power SYBR Green (TaKaRa, Dalian, China). PCR primers were synthesized by Invitrogen (Carlsbad, CA, USA). GAPDH was measured as an internal control and the $2^{-\Delta\Delta CT}$ method was employed to determine the relative expression of CASC9.

Table I. Correlation between CASC9 expression and clinicopathologic features of ESCC.

			CASC9 expression		
Parameters	**Group**	**Total**	**High**	**Low**	***p***
Age (years)	< 60	59	28	31	0.390
	≥ 60	69	38	31	
Gender	Male	77	37	40	0.329
	Female	51	29	22	
Tumor size	< 4 cm	82	39	43	0.226
	≥ 4 cm	46	27	19	
Histological grade	G1	90	42	48	0.088
	G2+G3	38	24	14	
Tumor stage	T1-T2	76	32	44	0.010
	T3-T4	52	34	18	
Lymph nodes metastasis	Absence	71	29	42	0.007
	Presence	57	37	20	
Clinical stage	I-II	83	36	47	0.012
	III-IV	45	30	15	

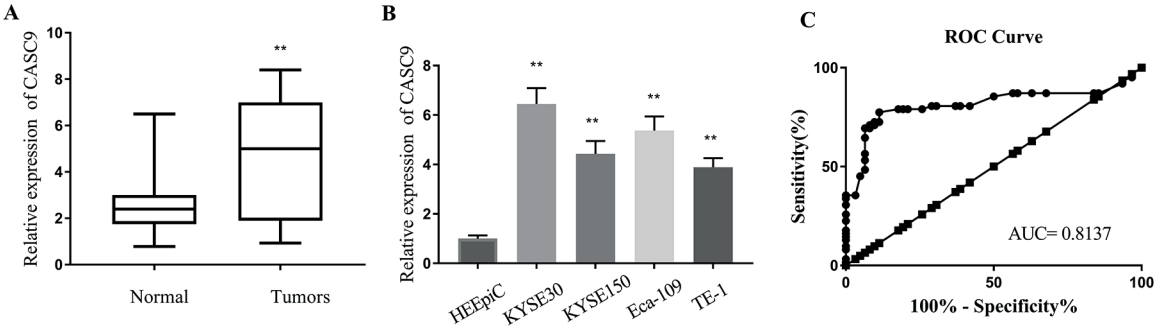

Figure 1. The expression of CASC9 is upregulated in ESCC tissues and cell lines. ***(A)*** CASC9 expression in ESCC tissue and adjacent tissue. ***(B)*** Representative qRT-PCR results of CASC9 in ESCC cell lines and one normal human esophageal epithelial cell line (HEEpiC). ***(C)*** ROC curve analysis illustrated that CASC9 was a potential biomarker for discriminating ESCC tissues from normal esophageal tissues. (AUC = 0.814, 95% CI; 0.730-0.898). $^{**}p < 0.01$, $^{*}p < 0.05$.

Cell Viability Assay

Cell viability was assessed by Cell Counting Kit (CCK)-8 kit (Tongren, Shanghai, China). The cell numbers were evaluated by measurement of absorbance at 450 nm. The cell growth rate was calculated.

Migration and Invasion Assays

Transwell chamber was used to detected the ability of ESCC cell migration and invasion. The procedure was described as previous study[19].

Western Blot Assay

Western blot was used to detect the expression levels of EMT-related markers. The procedures were performed as described previously[20].

Statistical Analysis

All data analyses were performed using SPSS 19.0 software (SPSS, Armonk, NY, USA). Data were expressed as mean ± standard error of the mean (SD). For continuous variables, Student's *t*-test was performed. x^2-test was used to compare the categorical variables. Receiver-operating characteristic (ROC) was uses to assess the potential value of CASC9 for ESCC diagnosis. Survival curves were generated by Kaplan-Meier method. The Cox proportional hazards model for multivariate survival analysis was used to assess predictors related to survival. Differences were considered statistically significant when $p < 0.05$.

Results

The Expression of CASC9 in ESCC Tissues and its Diagnostic Value

First, we determined the expression of CASC9 in 128 cases of ESCC tissues and corresponding nontumor tissues. As shown in Figure 1A, the results showed that CASC9 expression was significantly higher in ESCC tissues than that in adjacent normal tissues ($p <$

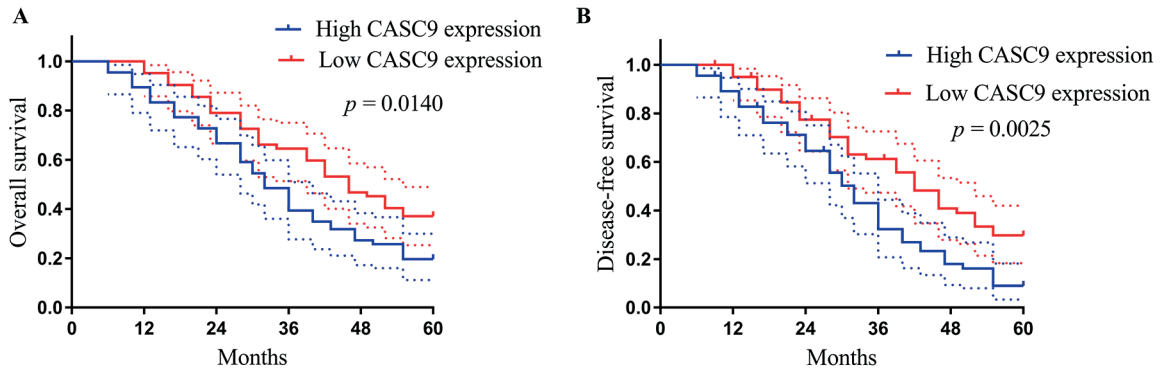

Figure 2. Kaplan-Meier curves of the OS and DFS of 128 ESCC patients. (A) OS rate in patients with high CASC9 expression was significantly lower than that in patients with low CASC9 expression. (B) DFS rate in patients with high CASC9 expression was significantly lower than that in patients with low CASC9 expression.

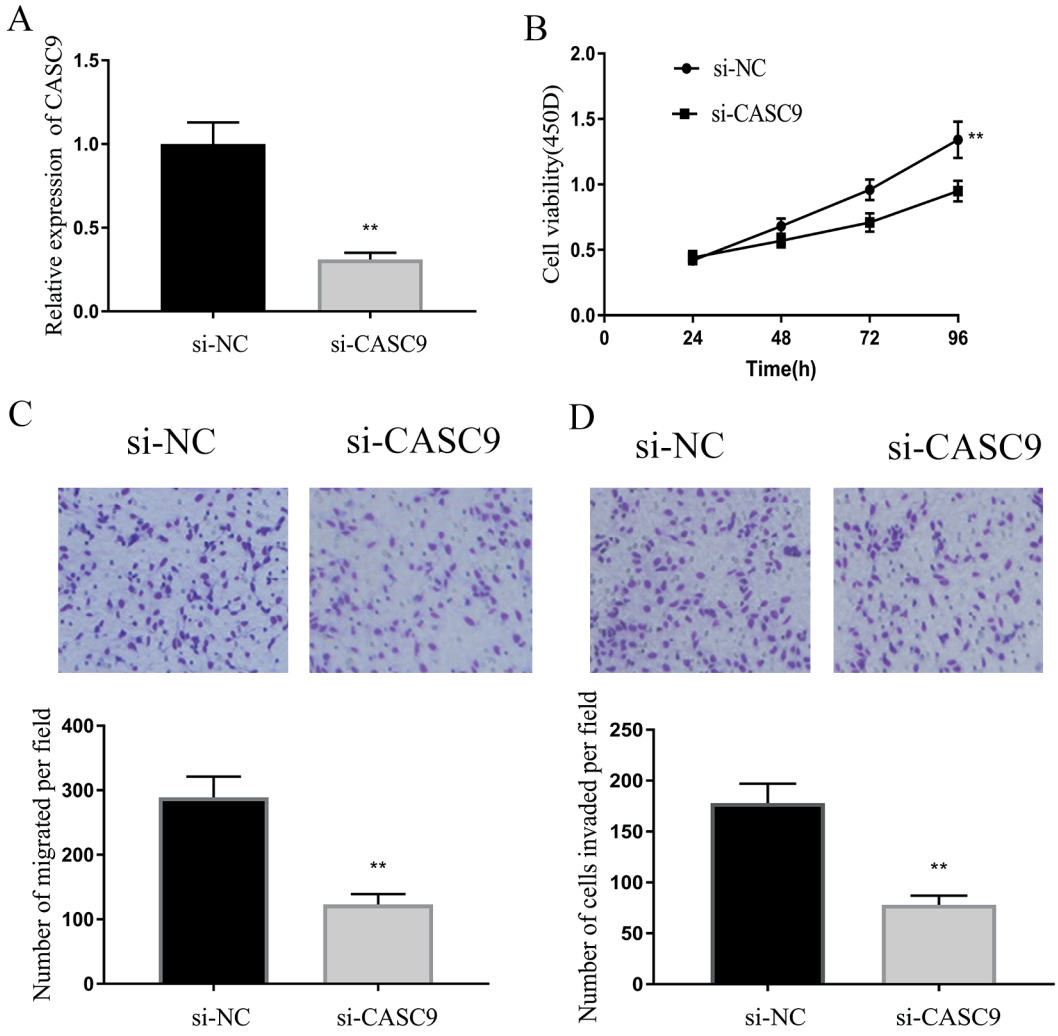

Figure 3. Effect of CASC9 on cell proliferation, invasion and migration. ***(A)*** Expression levels of CASC9 were tested by RTqPCR in Eca-109 cells transfected with si-CASC9 or si-NC. ***(B)*** Cell proliferation of Eca-109 cells was detected by CCK-8. ***(C, D)*** The migratory and invasive abilities of Eca-109 cells after transfection with si-CASC9 or si-NC were evaluated using transwell assays. $^{**}p < 0.01$, $^{*}p < 0.05$.

0.01). Moreover, we also found that CASC9 expression in ESCC cell lines (KEYSE30, KEYSE150, Eca-109, TE-1) was higher than that in HEEpiC (Figure 1B). Subsequently, we performed ROC curve to assess the capability of CASC9 to differentiate ESCC tissues from normal esophageal tissues. As shown in Figure 1C, the results showed that the area under the curve (AUC) was 0.814 (95% CI, 0.730-0.898). The optimal cutoff value was indicated at 46.5, with a sensitivity of 78.11% and a specificity of 95.34%.

Association of CASC9 Expression with Clinicopathological Features of ESCC Patients

To identify the clinical relevance of CASC9 expression in ESCC, association between CASC9 expression and clinicopathological parameters was evaluated. The 128 ESCC patients were classified into either the low CASC9 expression group (N = 62) or the high CASC9 expression group (N = 66) according to the median CASC9 level. Subsequently. We observed that over expression of CASC9 was significantly associated with tumor stage ($p = 0.010$), lymph nodes metastasis ($p = 0.007$) and clinical stage ($p = 0.012$, Table I). However, other clinical parameters were not found correlated with CASC9 expression.

Prognostic Values of CASC9 Expression in ESCC

Then, we analyzed the overall survival using the Kaplan-Meier approach, with the statistical analysis performed using the log-rank test. We indicated

Table II. Univariate and multivariate analysis of prognostic factors in OS.

	Univariate analysis		Multivariate analysis	
Variables	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age (years)	1.322(0.783-1.732)	0.271	-	-
Gender	1.673(0.583-1.946)	0.177	-	-
Tumor size	1.488(0.842-1.674)	0.139	-	-
Histological grade	1.653(0.829-2.231)	0.093	-	-
Tumor stage	3.674(1.453-5.774)	0.013	3.265(1.183-4.673)	0.018
Lymph nodes metastasis	3.923(1.673-7.932)	0.004	3.163(1.238-6.785)	0.008
Clinical stage	3.138(1.231-5.597)	0.016	2.362(1.032-4.113)	0.023
CASC9 expression	4.373(1.468-7.382)	0.001	3.193(1.139-5.332)	0.007

that ESCC patients with high CASC9 expression had shorter overall survival(OS) than those with low CASC9 expression ($p = 0.0140$) (Figure 2A). Further analysis with disease-free survival (DFS) also showed that ESCC patients with high CASC9 expression level had distinctly shorter DFS than patients with low CASC9 expression level ($p = 0.0025$, Figure 2B). To further explore the prognostic value of CASC9, the univariate and multivariate Cox regression analyses were performed. Univariate analysis showed that CASC9 expression levels were significantly correlated with OS and DFS (Table II and III). Further multivariate analysis confirmed that high CASC9 expression was a significant independent predictor of poor OS and DFS in ESCC (Table II and III).

CASC9 Silencing Inhibits Cell Proliferation, Invasion and Migration in ESCC Cells

To evaluate the effects of CASC9 on ESCC cell proliferation ability, si-CASC9 was stably introduced into Eca-109 cells. The effect of knockdown of CASC9 in cells was confirmed by qRT-PCR (Figure 3A). The results of CCK-8 showed that the proliferation rate of cells was markedly decreased by the transfection of si-CASC9 compared to the negative control ($p < 0.05$, Figure 3B). Next, we investigated the roles of CASC9 in ESCC cells metastasis. The results indicated that down-regulation of CASC9 could significantly decreased migration (Figure 3C) and invasion (Figure 3D) of Eca-109 cells. Taken together, we revealed that knockdown of CASC9 inhibited ESCC cell proliferation and metastasis.

Down-Regulation of CASC9 Suppresses EMT in ESCC

It is well recognized that EMT plays a critical role in ESCC cell migration and invasion[21]. Thus, we investigated whether CASC9 suppressed ESCC cell metastasis through regulating EMT. Western blot was performed to detect the expression levels of EMT-related markers. As shown in Figure 4, the results showed that suppressed CASC9 expression resulted in increased E-cadherin expression and decreased Fibronectin, Vimen-

Table III. Univariate and multivariate analysis of prognostic factors in DFS.

	Univariate analysis		Multivariate analysis	
Variables	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age (years)	1.324(0.785-1.896)	0.173	-	-
Gender	1.473(0.674-1.891)	0.144	-	-
Tumor size	1.324(0.893-1.725)	0.094	-	-
Histological grade	1.739(0.933-2.321)	0.079	-	-
Tumor stage	3.742(1.573-5.502)	0.013	2.984(1.218-4.328)	0.016
Lymph nodes metastasis	4.193(1.483-7.329)	0.007	3.251(1.219-5.672)	0.014
Clinical stage	3.554(1.289-5.193)	0.011	2.893(1.432-4.231)	0.019
CASC9 expression	4.329(1.483-6.239)	0.002	3.783(1.293-5.482)	0.005

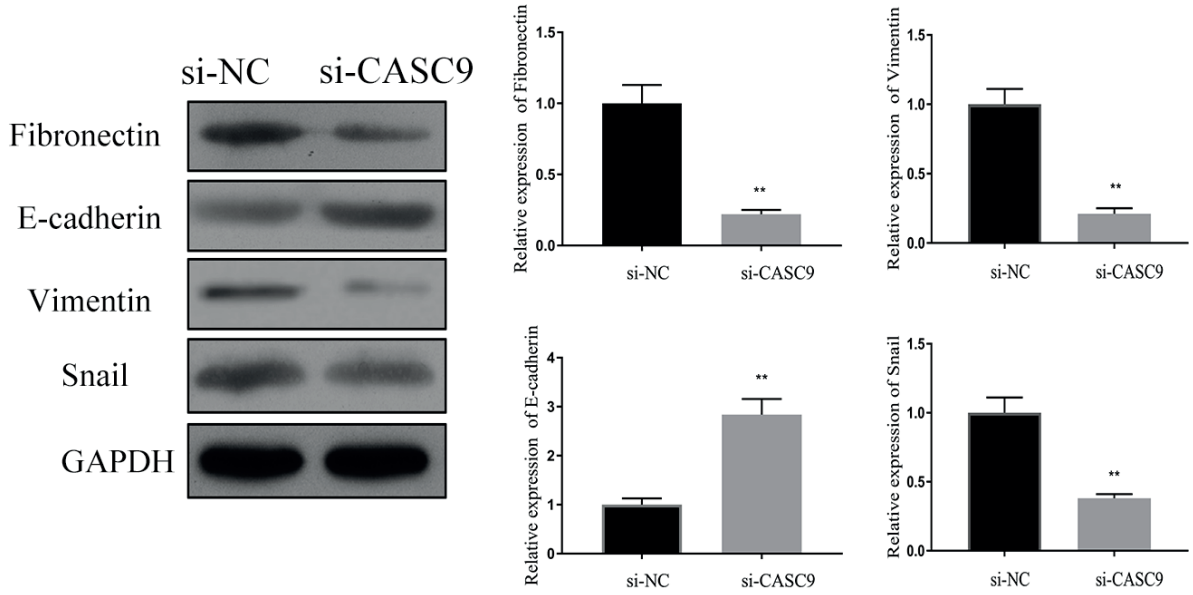

Figure 4. Knockdown of CASC9 suppressed EMT in Eca-109 cells. Fibronectin, Vimentin, E-cadherin and Snail protein expression levels in Eca-109 cells transfected with si-NC and si-CASC9 were analyzed by using Western blot. $^{**}p < 0.01$, $^{*}p < 0.05$.

tin and Snail expression. Therefore, these results revealed that suppressing CASC9 expression affected the EMT signaling pathway.

Discussion

As a novel biomarker, the potential roles of long non-coding RNAs as diagnostic and prognostic biomarkers have been extensively identified in several tumors[22-24]. In this study, we detected the expression levels of CASC9 in ESCC tissues and cell lines. We found that CASC9 expression was significantly up-regulated in both ESCC tissues and cell lines. These results were in line with the data of the RNA-seq analysis by Pan et al[16]. Next, we firstly performed ROC to judge the diagnostic value of CASC9 and our results showed that CASC9 was useful marker for discriminating ESCC tissues from normal tissues. Then, we showed that increased CASC9 expression was correlated with tumor stage, lymph nodes metastasis and clinical stage in ESCC. Furthermore, the survival analysis revealed that the patients with high expression of CASC9 had significantly worse OS and DFS. Further Cox regression analysis confirmed the expression of CASC9 was an independent factor for both OS and DFS in ESSC patients. These results suggested that CASC9 could be used as a potential predictor of diagnosis and prognosis in ESCC. Recently, the expression and biological function of CASC9 have been explored in several tumors. For instance, Shang et al[18] found that the expression of CASC9 was significantly up-regulated in gastric cancer and its silence inhibited proliferation and promoted cell apoptosis in gastric cancer cells. Su et al[17] reported that high CASC9 was associated with poor prognosis of nasopharyngeal carcinoma patients. Functional experiment showed that CASC9 promoted nasopharyngeal carcinoma cell growth via stabilizing HIF1α. Wu et al[25] indicated that high expression of CASC9 was found in ESCC tissues and associated with poor prognosis in ESCC patients. *In vivo* and *in vitro* assays showed that CASC9 served as an oncogene by negatively regulating PDCD4 expression through recruiting EZH2. In our present study, we also found down-regulation of CASC9 suppressed ESCC cells proliferation and metastasis. These results were in line with previous paper[25]. However, to be honest, we didn't perform *in vivo* to confirm our results about the tumor-promotive effect of CASC9 in ESCC.

EMT is an important cellular mechanism in embryonic development, tissue repair, and disease[26]. It has been confirmed that activation of EMT leads to increased cell migration and invasion, resulting in tumor aggressiveness[27]. Recently, more and more studies showed that lncRNAs function as tumor suppressors or oncogenes by affecting EMT signal ways[28,29]. Thus, our attention focused on the association between CASC9 and

EMT. Functional assays demonstrated CASC9 may exert functions in migration and invasion of ESCC cells through modulating EMT. However, further *in vitro* and *in vivo* assays were needed to explore the specific role of ESCC in EMT.

Conclusions

Our study provides evidence that CASC9 may be a predictive biomarker for ovarian cancer prognosis and diagnosis. Furthermore, we demonstrate that CASC9 induces cell proliferation and EMT in ESCC. In the future, CASC9 could be a potential therapeutic target for ESCC.

Conflict of Interest

The Authors declare that they have no conflict of interest.

References

1) Njei B, McCarty TR, Birk JW. Trends in esophageal cancer survival in United States adults from 1973 to 2009: a SEER database analysis. J Gastroenterol Hepatol 2016; 31: 1141-1146.
2) Shah MA, Kurtz RC. Upper gastrointestinal cancer predisposition syndromes. Hematol Oncol Clin North Am 2010; 24: 815-835.
3) Qi YJ, Chao WX, Chiu JF. An overview of esophageal squamous cell carcinoma proteomics. J Proteomics 2012; 75: 3129-3137.
4) Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst 2005; 97: 142-146.
5) Enzinger PC, Mayer RJ. Esophageal cancer. N Engl J Med 2003; 349: 2241-2252.
6) Kang X, Chen K, Li Y, Li J, D'Amico TA, Chen X. Personalized targeted therapy for esophageal squamous cell carcinoma. World J Gastroenterol 2015; 21: 7648-7658.
7) Ulitsky I, Bartel DP. lincRNAs: genomics, evolution, and mechanisms. Cell 2013; 154: 26-46.
8) Geisler S, Coller J. RNA in unexpected places: long non-coding RNA functions in diverse cellular contexts. Nat Rev Mol Cell Biol 2013; 14: 699-712.
9) Han D, Wang M, Ma N, Xu Y, Jiang Y, Gao X. Long noncoding RNAs: novel players in colorectal cancer. Cancer Lett 2015; 361: 13-21.
10) Schmitt AM, Chang HY. Long noncoding RNAs in cancer pathways. Cancer Cell 2016; 29: 452-463.
11) Wang X, Li M, Wang Z, Han S, Tang X, Ge Y, Zhou L, Zhou C, Yuan Q, Yang M. Silencing of long noncoding RNA MALAT1 by miR-101 and miR-217 inhibits proliferation, migration, and invasion of esophageal squamous cell carcinoma cells. J Biol Chem 2015; 290: 3925-3935.
12) Ren ZP, Chu XY, Xue ZQ, Zhang LB, Wen JX, Deng JQ, Hou XB. Down-regulation of lncRNA MIR31HG correlated with aggressive clinicopathological features and unfavorable prognosis in esophageal squamous cell carcinoma. Eur Rev Med Pharmacol Sci 2017; 21: 3866-3870.
13) Tan DSW, Chong FT, Leong HS, Toh SY, Lau DP, Kwang XL, Zhang X, Sundaram GM, Tan GS, Chang MM, Chua BT, Lim WT, Tan EH, Ang MK, Lim TKH, Sampath P, Chowbay B, Skanderup AJ, DasGupta R, Iyer NG. Long noncoding RNA EGFR-AS1 mediates epidermal growth factor receptor addiction and modulates treatment response in squamous cell carcinoma. Nat Med 2017; 23: 1167-1175.
14) Tong YS, Wang XW, Zhou XL, Liu ZH, Yang TX, Shi WH, Xie HW, Lv J, Wu QQ, Cao XF. Identification of the long non-coding RNA POU3F3 in plasma as a novel biomarker for diagnosis of esophageal squamous cell carcinoma. Mol Cancer 2015; 14: 3.
15) Hao Y, Wu W, Shi F, Dalmolin RJ, Yan M, Tian F, Chen X, Chen G, Cao W. Prediction of long noncoding RNA functions with co-expression network in esophageal squamous cell carcinoma. BMC Cancer 2015; 15: 168.
16) Pan Z, Mao W, Bao Y, Zhang M, Su X, Xu X. The long noncoding RNA CASC9 regulates migration and invasion in esophageal cancer. Cancer Med 2016; 5: 2442-2447.
17) Su X, Li G, Liu W. The long noncoding rna cancer susceptibility candidate 9 promotes nasopharyngeal carcinogenesis via stabilizing HIF1α. DNA Cell Biol 2017; 36: 394-400.
18) Shang C, Sun L, Zhang J, Zhao B, Chen X, Xu H, Huang B. Silence of cancer susceptibility candidate 9 inhibits gastric cancer and reverses chemoresistance. Oncotarget 2017; 8: 15393-15398.
19) Li J, Zhu SC, Li SG, Zhao Y, Xu JR, Song CY. TKTL1 promotes cell proliferation and metastasis in esophageal squamous cell carcinoma. Biomed Pharmacother 2015; 74: 71-76.
20) Zhang W, He W, Gao J, Wang Y, Zang W, Dong Z, Zhao G. The long noncoding RNA CASC2 inhibits tumorigenesis through modulating the expression of PTEN by targeting miR-18a-5p in esophageal carcinoma. Exp Cell Res 2017; 361: 30-38.
21) Niwa Y, Yamada S, Koike M, Kanda M, Fujii T, Nakayama G, Sugimoto H, Nomoto S, Fujiwara M, Kodera Y. Epithelial to mesenchymal transition correlates with tumor budding and predicts prognosis in esophageal squamous cell carcinoma. J Surg Oncol 2014; 110: 764-769.
22) Evans JR, Feng FY, Chinnaiyan AM. The bright side of dark matter: lncRNAs in cancer. J Clin Invest 2016; 126: 2775-2782.
23) Zhao QS, Li L, Zhang L, Meng XW, Li LL, Ge XF, Li ZP. Over-expression of lncRNA SBF2-AS1 is associated with advanced tumor progression and

poor prognosis in patients with non-small cell lung cancer. Eur Rev Med Pharmacol Sci 2016; 20: 3031-3034.

24) Liang W, Lv T, Shi X, Liu H, Zhu Q, Zeng J, Yang W, Yin J, Song Y. Circulating long noncoding RNA GAS5 is a novel biomarker for the diagnosis of nonsmall cell lung cancer. Medicine (Baltimore) 2016; 95: e4608.

25) Wu Y, Hu L, Liang Y, Li J, Wang K, Chen X, Meng H, Guan X, Yang K, Bai Y. Up-regulation of lncRNA CASC9 promotes esophageal squamous cell carcinoma growth by negatively regulating PDCD4 expression through EZH2. Mol Cancer 2017; 16: 150.

26) Li L, Li W. Epithelial-mesenchymal transition in human cancer: comprehensive reprogramming of metabolism, epigenetics, and differentiation. Pharmacol Ther 2015; 150: 33-46.

27) Davis FM, Stewart TA, Thompson EW, Monteith GR. Targeting EMT in cancer: opportunities for pharmacological intervention. Trends Pharmacol Sci 2014; 35: 479-488.

28) Shen L, Chen L, Wang Y, Jiang X, Xia H, Zhuang Z. Long noncoding RNA MALAT1 promotes brain metastasis by inducing epithelial-mesenchymal transition in lung cancer. J Neurooncol 2015; 121: 101-108.

29) Wu J, Zhang J, Shen B, Yin K, Xu J, Gao W, Zhang L. Long noncoding RNA lncTCF7, induced by IL-6/STAT3 transactivation, promotes hepatocellular carcinoma aggressiveness through epithelial-mesenchymal transition. J Exp Clin Cancer Res 2015; 34: 116.