MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2017; 23: 5246-5253
DOI: 10.12659/MSM.904912

Received: 2017.04.18
Accepted: 2017.06.27
Published: 2017.11.03

Expression of Heat Shock Protein-27 (Hsp27) and P38MAPK in Esophageal Squamous Cell Carcinoma

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Source of support: This research was supported by Natural Science Foundation, China (No.81360303). Title: Research of Screening Different Protein in Esophageal Squamous Cell Carcinoma and Molecular Biomarkers

Background: Esophageal squamous cell carcinoma (ESCC) is a worldwide concern. This study looked at the relationship between the expression of differential proteins and the clinicopathological data and survival rate of ESCC patients to identify potential tumor markers for the growth and metastasis of ESCC.

Material/Methods: This study included 162 patients who underwent surgical excision for management of ESCC. Fresh ESCC tissue and adjacent normal tissue specimens were collected. Protein expressions were detected by western blotting. The expression of Hsp27 and P38MAPK were detected by immunohistochemistry in formalin-fixed paraffin embedded primary tissue specimens.

Results: The rate of positive Hsp27 and P38MAPK expression in ESCC tissue were higher than in normal esophageal tissue ($p<0.05$). The expression of P38MAPK was related to the depth of infiltration ($p<0.05$). The expression of Hsp27 was correlated with lymph node metastasis ($p<0.05$), but not with age, depth of infiltration, or tumor size. ROC were plotted to estimate the significance of the diagnosis: for Hsp27, AUC=0.735 ($p<0.05$), for P38MAPK, AUC=0.882 ($p<0.05$).

Conclusions: The expression of Hsp27 and P38MAPK plays a role in ESCC development. Hsp27 and P38MAPK could be used as prognostic factors in ESCC.

MeSH Keywords: **Esophageal Neoplasms • HSP27 Heat-Shock Proteins • Mitogen-Activated Protein Kinase 13**

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/904912

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Background

Esophageal squamous cell carcinoma (ESCC) has caused worldwide public health concern. The number of ESCC sufferers has increased gradually in recent years. The incidence rate varies in different physiographical regions, nations, and races. China has a high incidence of ESCC with a high mortality rate for ESCC patients. The Kazak population in northwest China has been reported to exhibit the highest incidence of ESCC. The mortality rate for esophageal cancer is 13.05 per 100,000 population in the Xinjiang region of China [1]. Zhang et al. [2,3] studied the differentially expressed proteins between human normal esophageal epithelial cells (NEEC) and ESCC cells; the differential protein expressions between NEEC and ESCC cells were identified by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS).

Heat shock protein-27 (Hsp27) is a member of a family of proteins.Their intracellular expression modulates the ability of cells to respond to several types of injury, heat shock, oxidative stress, and other unfavorable conditions. Besides its chaperone function, Hsp27 has also been shown to have an anti-apoptotic role by inhibition of caspase-dependent apoptosis, preventing a wide variety of apoptotic agents from causing cell death. Because over-expression of Hsp27 correlates with poor survival in ESCC patients, it may also be of importance.

The involvement of P38MAPK in cancer has been widely described. However, its role as an oncogene or tumor suppressor is unclear. Recently, numerous clinical trials have been initiated to use P38MAPK inhibitors in combination with chemotherapy for various types of cancer. As chemotherapy is a powerful inducer of P38MAPK activity, which in turn results in increased HAS2 activity and hyaluronic acid (HA) deposition, the use of either P38 or HA inhibitors could significantly dampen the cancer-promoting activity of the tumor microenvironment.

This study aimed to determine the expressions of Hsp27 and P38MAPK in ESCC by using western blotting and immunohistochemistry, and to statistically analyze the expressions of Hsp27 and P38MAPK, and determine the related clinicopathological characteristics of ESCC.

Material and Methods

Study materials

The study was carried out at the Affiliated Hospital of Xinjiang Medical University. Fresh ESCC tissue and adjacent normal tissue specimens were collected from patients between 2014 and 2015. Paraffin-embedded biopsy samples were selected from 162 patients with ESCC between 2012 and 2015. All specimens were obtained after surgery. Specimens were identified by immunohistochemical methods. Of the 162 patients, 108 were males and 54 were females; ages ranged from 38.0 to 83.0 years, with the average age of 63.5±9.0 years; 67 patients were of Kazak ethnicity and 95 patients were of Han ethnicity; 107 patients experienced lymphatic metastasis and 55 patients did not. Additionally, we enrolled 50 individuals for normal tissue specimens and recorded basic patient information including sex, age, and ethnicity. Specimens were collected and analyzed by two experienced pathologists. The study was funded by the Natural Science Foundation of Xinjiang and was reviewed by the medical ethics committee of the hospital. All participants acknowledged and signed the informed consent documents.

Study design

Total protein of the ESCC tissue was evaluated by BCA protein assay (CWBIO, Beijing, China). Then 30 µg of the ESCC tissue protein were analyzed by NuPAGE 4–12% Bis-Tris polyacrylamide gels (Invitrogen, Carlsbad, CA, USA) that were transferred to polyvinylidene fluoride membranes (Invitrogen). The membranes were incubated overnight with polyclonal rabbit anti-Hsp27-antibody, polyclonal rabbit anti-P38MAPK-antibody (Bioss, Beijing, China), at 1: 1,000 dilution, respectively. The analysis was performed with NBT/BCIP staining. Protein expression was normalized to the quantity of beta-actin. The signal and grayscale values were visualized and analyzed by using ImageJ software, and grayscale value ratios were calculated. SP immunohistochemical method was used to detect the expression of Hsp27 and P38MAPK. The immunohistochemical EnVision-2 footwork method was used to detect the expression of Hsp27 and P38MAPK.

Immunohistochemical EnVision two footwork methods were used to determine the protein expression of Hsp27 and P38MAPK. The procedure was as follows: paraffin sections were dewaxed step by step, hydrated in water, incubated with 30 mL/L H_2O_2 (Bioss, Beijing, China) for 20 minutes at room temperature, and rinsed with PBS. The slices were placed in citrate buffer salt at pH 6.0; the repair antigen was added, and heated for 20 minutes in a microwave (temperature controlled at 95–100°C). The slices were then cooled to room temperature and rinsed with PBS. The antibody was then added and placed in the refrigerator at 4°C overnight. The slices were washed using the same method; DAB chromogenic reagent was added and the slices were placed in a wet box. Termination of the chromogenic reaction was achieved with tap water; then slice Wood grain redyeing, hydrochloric acid alcohol differentiation back to blue, and dehydration sealing. Western blotting was as follows: protease inhibitors (Bioss, Beijing, China) were added to cell lysates that were then placed on ice for 20 minutes. Lysates were then centrifuged at 14,000 rpm for 10

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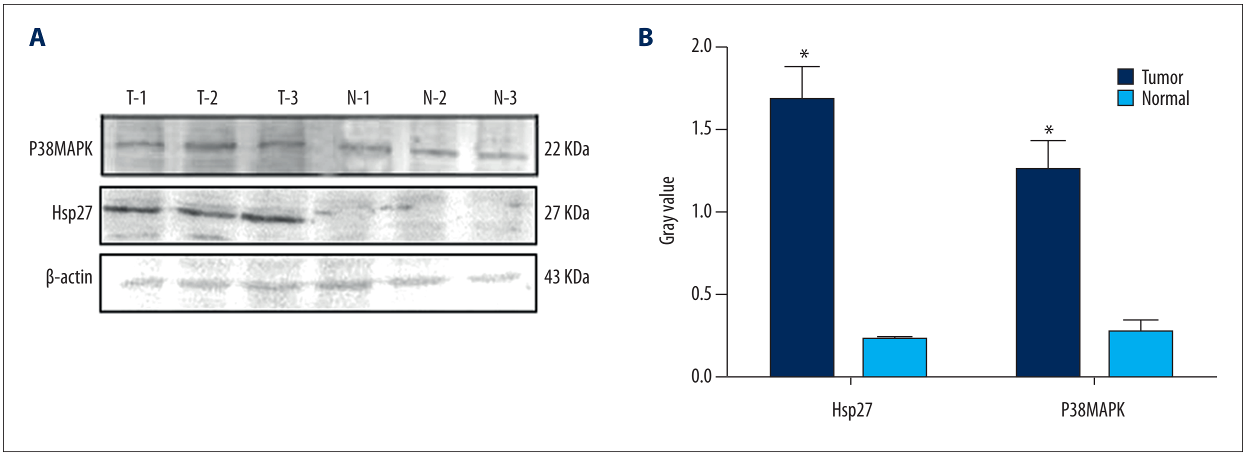

Figure 1. (**A**) The wetern blotting bands of Hsp27 and P38MAPK in ESCC tissue. (**B**) The expression of Hsp27 and P38MAPK in ESCC tissue (western blotting), * P<0.05 *vs.* the normal tissue.

minutes at 4°C; protein (50 ug) was boiled for five minutes and separated by SDS-PAGE (Bioss, Beijing, China). Gels were transferred to a polyvinylidene fluoride PVDF membrane and blocked for one hour at room temperature. Blots were incubated with rabbit polyclonal antibody against PARD3 (Abcam, USA) or β-actin (Bioss, Beijing, China) at 4°C overnight, followed by incubation with the secondary antibody (Bioss, Beijing, China) at room temperature for one hour. A chemiluminescent substrate (CWBIO, Beijing, China) was added to visualize the specific bands. Quantity One software was used to quantify the intensity of each band and β-actin was used as the control. Positive Hsp27 and P38MAPK expression was indicated by tan or brown granular particles in the cytoplasm. Expression in normal esophageal tissue was used as a control group.

Statistical analysis

Statistical analyses were conducted using SPSS17.0 software for analyzing sex, age, ethnicity, size of tumor, degree of differentiation, depth of infiltration, and lymphatic metastasis; we used the χ^2 test and *t*-test. Inspection level $\alpha=0.05$, $p<0.05$ was considered statistically significant.

Results

Expression of Hsp27 and P38MAPK in ESCC and normal esophageal tissue by western blotting

Western blotting results showed that the grayscale value ratios of Hsp27 in the ESCC tissue (case 3) were 1.66, 1.33, and 2.03. The grayscale value ratios of Hsp27 in normal tissue were 0.26, 0.25, and 0.17. These results showed that the expressions of Hsp27 had an increasing trend in the ESCC tissue compared with that of normal tissue ($p<0.05$).

Western blotting results showed that the grayscale value ratios of P38MAPK in the ESCC tissue (case 3) were 1.21, 1.41, and 0.98. The grayscale value ratios of P38MAPK in the normal tissue were 0.35, 0.25, and 0.19. These results showed that the expressions of P38MAPK had an increasing trend in the ESCC tissue compared with that of normal tissue ($p<0.05$) (Figure 1).

Expression of Hsp27 and P38MAPK in ESCC and normal esophageal tissue by immunohistochemical method

Immunohistochemical results showed that the rate of expression of Hsp27 in esophageal cancer tissue compared to normal tissue was 71.0% (115/162) versus 24.0% (12/50) (Figures 2–5). The difference in rates was statistically significant ($p<0.05$) (Table 1).

Immunohistochemical results for the expression of P38MAPK in ESCC are shown in Figures 6–9. The rate of expression of P38MAPK in esophageal cancer tissue compared to normal tissue was 93.2% (151/162) versus 68.0% (34/50). The difference in rates was statistically significant ($p<0.05$) (Table 2).

Significance of the diagnosis by ROC curve analysis

According to the rate of expression of Hsp27 and P38MAPK in esophageal cancer tissue and normal tissue, ROC were plotted to estimate the significance of the diagnosis: Hsp27, AUC=0.735 (95.0% CI, 0.655–0.815), SE=0.04 with a significance level of $p<0.001$; and P38MAPK, AUC=0.882 (95.0% CI, 0.842–0.962), SE=0.03 with a significance level of $p<0.001$ (Figure 10).

Relationship between Hsp27 and P38MAPK expression and clinical pathological parameters

Hsp27 expression in patients without lymphatic metastasis and in patients with lymphatic metastasis was 62.6% and

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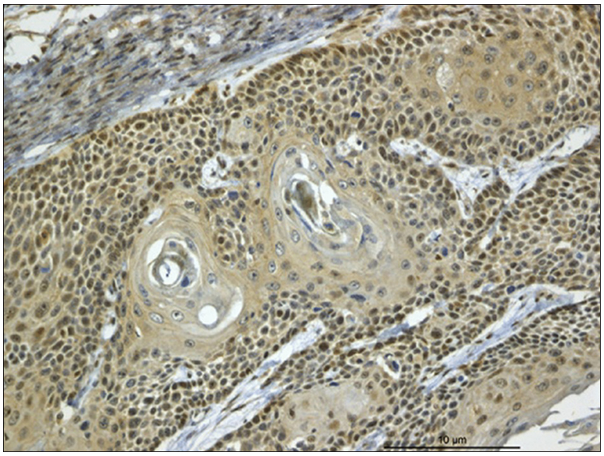

Figure 2. Positive expression of Hsp27 in esophageal squamous cell carcinoma (×100).

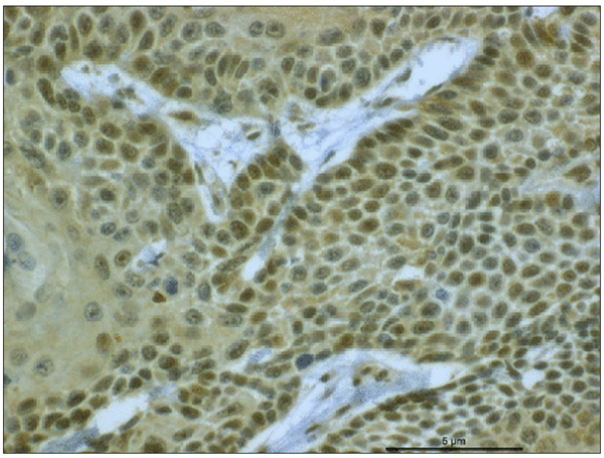

Figure 3. Positive expression of Hsp27 in esophageal squamous cell carcinoma (×400).

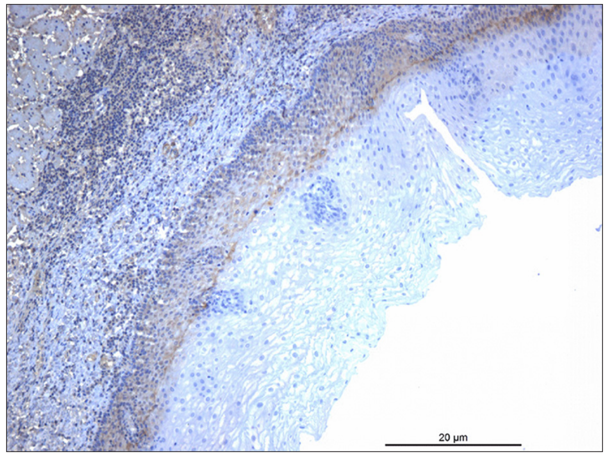

Figure 4. Negative expression of Hsp27 in esophageal squamous cell carcinoma (×100).

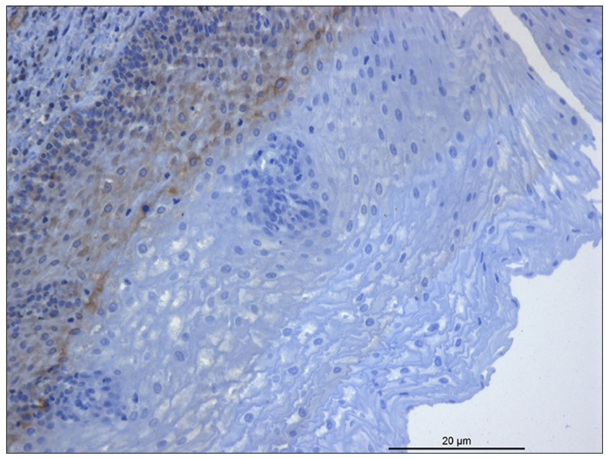

Figure 5. Negative expression of Hsp27 in esophageal squamous cell carcinoma (×400).

Table 1. Hsp27 protein expression in esophageal cancer and normal esophageal tissues.

Pathological characteristic	Total cases	Positive	Negative	Positive rate (%)	χ^2	*P* value
Cancerous tissue	162	115	47	71.0	35.120	<0.01
Normal tissue	50	12	38	24.0		

87.3%, respectively. The difference was statistically significant ($p<0.05$), which shows that Hsp27 expression was higher in patients with lymphatic metastasis. Hsp27 expression in ESCC was not correlated with sex, age, nationality, ethnicity, tumor size, or depth of infiltration. There was no significant difference in expression ($p>0.05$) (Table 3).

P38MAPK expression in different depths of infiltration was 80.0%, 96.8%, 96.3%, and 88.0%, respectively. The difference was statistically significant ($p<0.05$). P38MAPK expression in Kazak ethnic patients and Han ethnic patients was 91.0% and 94.7%, respectively. There was no statistical significant difference ($p>0.05$). P38MAPK expression in patients without lymphatic metastasis and in those with lymphatic metastasis was 90.7% and 98.2%, respectively. Although P38MAPK expression was higher in patients without lymphatic metastasis, there was no statistical significant difference ($p>0.05$). These results indicate that P38MAPK expression in ESCC has no relationship with sex, age, ethnicity, differentiation degree, tumor size, or lymphatic metastasis ($p>0.05$) (Table 4).

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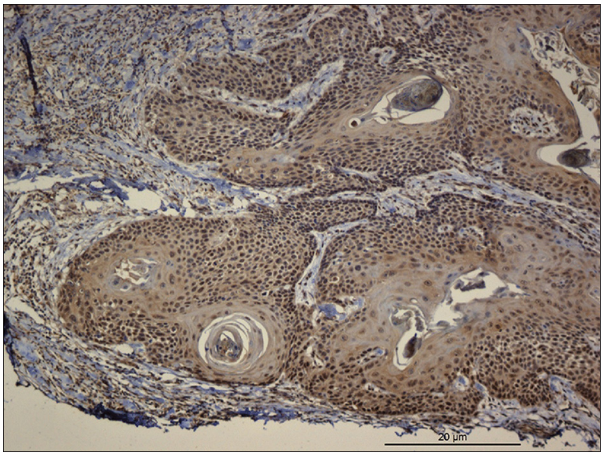

Figure 6. Positive expression of P38MAPK in esophageal squamous cell carcinoma (×100).

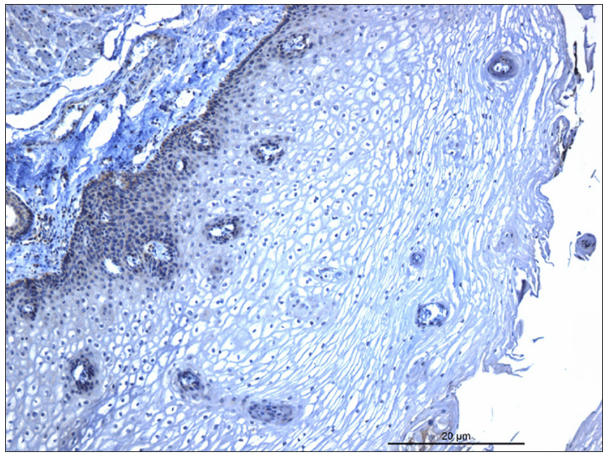

Figure 8. Negative expression of P38MAPK in esophageal squamous cell carcinoma (×100).

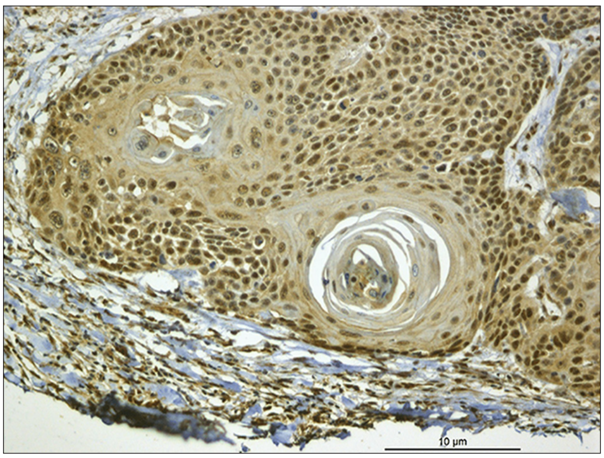

Figure 7. Positive expression of P38MAPK in esophageal squamous cell carcinoma (×400).

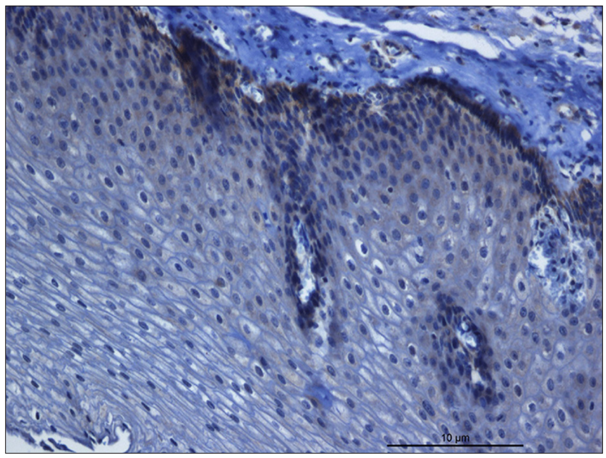

Figure 9. Negative expression of P38MAPK in esophageal squamous cell carcinoma (×400).

Table 2. P38MAPK protein expression in esophageal cancer and normal esophageal tissues.

Pathological characteristic	Total cases	Positive	Negative	Positive rate (%)	χ^2	*P* value
Cancerous tissue	162	151	11	93.2	21.849	<0.001
Normal tissue	50	34	16	68.0		

Discussion

Heat shock protein 27 (Hsp27) is a member of the heat shock protein family which has been linked to tumor progression and, most interestingly, to chemotherapy resistance in cancer patients. There is evidence showing a role for Hsp27 in the balance between tumor dormancy and tumor progression, mediated by tumor-vascular interactions [4]. Hsp27 function is associated with deleterious outcomes in cancer and is associated with the development of drug resistance [5]. Some studies have found that exogenous Hsp27 uniquely blocks differentiation of monocytes to dendritic cells. This suggests that endogenous Hsp27 has immunoregulatory activities which could contribute to immunopathology. It has been speculated that Hsp27 enhances the ability of migration and invasion of cancer cells by preventing dendritic cell maturation [6]. Blocking the expression of Hsp27 protein has become an important research direction in tumor targeted therapy [7,8]. The over-expression of Hsp27 has been detected in invasive tumor cells in breast carcinoma, oral squamous cell carcinoma, and pancreatic carcinoma [9–11]. Some studies have also found that patients with upregulated expression of Hsp27 have better

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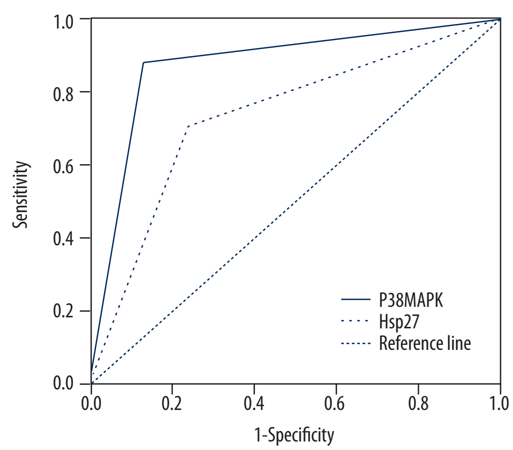

Figure 10. Receiver operating characteristic curve.

long-term prognosis for carcinoma [12,13]. Lambot et al. [14] found Hsp27 protein expression increased drastically from dysplastic lesions to invasive carcinoma, being highest in the less differentiated areas.

In our study, we identified Hsp27 as an important participant in ESCC lymphatic metastasis. We found Hsp27 expression was significantly upregulated in ESCC tissues. Our data showed evidence of a significantly elevated level of Hsp27 in ESCC than adjacent tissue. Hsp27 expression in ESCC was shown to be associated with patients' lymphatic metastasis. However, patient ethnicity had no effect on Hsp27 expression. These results indicate that Hsp27 plays a role in the carcinogenesis and development of ESCC. Further studies are needed to determine whether Hsp27 can be used as a pre-diagnosis indicator for ESCC; whether the expression of Hsp27 is closely related to drug resistance; and whether it can be used as a useful parameter to guide individual chemotherapy.

Mitogen-activated protein kinases (MAPKs) are involved in a variety of fundamental cellular processes, such as proliferation, differentiation, apoptosis, and survival. Previous studies have demonstrated activation of MAPKs pathways by pro-inflammatory cytokines in endothelial cells [15]. To the best of our knowledge, researchers have done very few studies on the relationship between P38MAPK and ESCC. P38MAPK (MAPK14) is a well-studied stress kinase that transmits numerous extracellular signals and is involved in multiple cellular processes.

Table 3. Correlation between Hsp27 expression and clinicopathological data.

Characteristic	Negative	Positive	Positive rate (%)	t/χ^2	*P* value
Age (yr)					
Mean value	64.77±9.07	62.92±8.96	–	1.184	0.238
Sex					
Male	29	79	73.1	0.734	0.463
Female	18	36	66.7		
Nationality					
Han	30	65	68.4	0.735	0.482
Kazakh	17	50	74.6		
Differentiation degree					
Moderate to high	35	88	71.5	0.077	0.840
Low	12	27	69.2		
Tumor size (cm)					
Mean value	2.82±1.88	3.03±1.85	–	–0.665	0.507
Depth of infiltration					
Mucosal & submucosa	8	12	60.0	1.338	0.294
Muscular layer	39	103	72.5		
Lymphatic metastasis					
No	40	67	62.6	10.723	0.001
Yes	7	48	87.3		

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Table 4. Correlation between P38MAPK expression and clinicopathological data.

Characteristic	Negative	Positive	Positive rate (%)	t/χ^2	*P* value
Age (yr)					
Mean value	65.45±8.45	63.31±9.05	–	0.761	0.448
Sex					
Male	5	103	95.4	2.390	0.182
Female	6	48	88.9		
Nationality					
Han	5	90	94.7	0.846	0.365
Kazakh	6	61	91.0		
Differentiation degree					
Moderate to high	10	113	91.9	1.449	0.463
Low	1	38	97.4		
Tumor size (cm)					
Mean value	2.14±1.12	3.03±1.89	–	−1.546	0.124
Depth of infiltration					
Submucosa	4	16	80.0	8.078	0.034
Muscular layer	2	61	96.8		
Adventitia	2	52	96.3		
Adjacent structure	3	22	88.0		
Lymphatic metastasis					
No	10	97	90.7	3.252	0.100
Yes	1	54	98.2		

The role of P38MAPK has been rigorously investigated in cancer. Originally proposed as a potential cancer suppressor [16], the role of P38MAPK in tumorigenesis, however, remains controversial. Recent studies of epithelial cells with disruption of P38MAPK have shown that its role in cancer cells is to suppress lung, liver, and colon tumor formation *in vivo* [17–19]. Over-expression of P38MAPK has been observed in hepatocellular carcinoma, lung adenocarcinoma, colorectal carcinoma, and head and neck squamous cell carcinoma [20–22].

In this study, we were able to establish a prognostic value for P38MAPK in human ESCC, where common P38MAPK over-expression correlated with advance tumor histology. The acquisition of migratory and invasive ability is a prerequisite for cancer cells to invade and metastasize. This process involves multiple intracellular cytoskeletal components and complex orchestration of biological pathways, often involving an intricate interplay between proteins. In the present study, we demonstrated that P38MAPK over-expression in ESCC was correlated with the depth of infiltration, suggesting that the detection of P38MAPK is valuable as a prognostic indicator of ESCC. However, other studies have reported conflicting results and more experiments are needed to confirm our findings. Identification of P38MAPK expression as the specific biomarker of ESCC could be an effective approach for determining the effect of treatment as well as the prognosis of tumors. At present, many trials have been initiated that use P38MAPK inhibitors in combination with chemotherapy for various types of cancer. In addition, hyaluronic acid (HA) is present as high and low molecular weight (HMW-HA, LMW-HA) polymers with LMW-HA generated by hyaluronidase-dependent fragmentation of HMW-HA. As chemotherapy is a powerful inducer of P38MAPK activity, the use of either P38 or HA inhibitors could significantly inhibit the cancer activity of the tumor microenvironment. From a therapeutic standpoint, the best approach to target HA-mediated tumor progression could be by blocking P38MAPK with pharmacological inhibitors, inhibiting HA synthesis targeting hyaluronidases, or disrupting HA-receptor interactions [23]. At present, fundamental research about effective methods of treatment of esophageal carcinoma is ongoing,

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and there still are many pending disputes and question needing to solve [24–26]. Further studies are needed in this area. In our study, we were able to show the importance of P38MAPK and its effect on ESCC cell migration.

Conclusions

The expression levels of Hsp27 and P38MAPK play a role in the carcinogenesis and development of ESCC. Hsp27 and P38MAPK could be used as prognostic indicators in ESCC. Over-expression of Hsp27 was associated with lymphatic metastasis in patients with ESCC. Our experiment showed that P38MAPK was related to the high incidence of ESCC in depth of infiltration. Hsp27 and P38MAPK may play a role in the progression of esophageal cancer. Furthermore, we identified Hsp27 and P38MAPK as specific biomarkers of ESCC. Further studies are needed to confirm Hsp27 and P38MAPK as prognostic indicators for the effect of treatment and tumor prognosis.

References:

1. Lv XP, Pu HW, Chen X et al: [Proteomic analysis of differentially expressed proteins in esophageal squamous cell carcinoma by MALDI-TOF-MS.] World Chinese Journal of Digestology, 2011; 19(36): 3682–86 [in Chinese]
2. Zhang Y, Zhang YL, Chen HM et al: Expression of Bmi-1 and PAI-1 in esophageal squamous cell carcinoma. World J Gastroenterol, 2014; 20(18): 5533–39
3. Zhang Y, Riao RY, Li H et al: Expression of Cofilin-1 and Transgelin in esophageal squamous cell carcinoma. Med Sci Monit, 2015; 21: 2659–65
4. Alvarez-Olmedo DG, Biaggio VS, Koumbadinga GA et al: Recombinant heat shock protein 27 (HSP27/HSPB1) protects against cadmium-induced oxidative stress and toxicity in human cervical cancer cells. Cell Stress Chaperones, 2017; 22(3): 357–69
5. Bakthisaran R, Tangirala R, Rao ChM: Small heat shock proteins: Role incellular functions and pathology. Biochim Biophys Acta, 2015; 1854: 291–319
6. Lucijanic M, Livun A, Tupek KM et al: Heat shock protein 27 (HSP27/HSPB1) expression is increased in patients with primary and secondary myelofibrosis and may be affecting their survival. Leuk Lymphoma, 2017; 58(10): 2497–2500
7. Sauvage F, Messaoudi S, Fattal E et al: Heat shock proteins and cancer: How can nanomedicine be harnessed? J Control Release, 2017; 248: 133–43
8. Nosareva OL, Ryazantseva NV, Stepovaya EA et al: [The role of heat shock proteins 27 and 70 in redox-dependent regulation of apoptosis in Jurkat tumor cells.] Biomed Khim, 2016; 62(6): 670–73 [in Russian]
9. Hadadi E, Zhang B, Baidžajevas K et al: Differential IL-1β secretion by monocyte subsets is regulated by Hsp27 through modulating mRNA stability. Sci Rep, 2016, 6: 39035
10. Fatemeh HS, Hassan MM, Mojtaba T et al: Anti-heat shock protein-27 antibody levels in women with breast cancer: Association with disease complications and two-year disease-free survival. Asian Pac J Cancer Prev, 2016; 17(10): 4655–59
11. Cordonnier T, Bishop JL, Shiota M et al: Hsp27 regulates EGF/β-catenin mediated epithelial to mesenchymal transition in prostate cancer. Int J Cancer, 2015; 136(6): 496–507
12. Ruge F, Gao Y, Wei C et al: Heat shock protein 27 is a potential indicator for response to YangZheng XiaoJi and chemotherapy agents in cancer cells. Int J Oncol, 2016, 49: 1839–47
13. Wang XW, Shi XH, Tong YS: The prognostic impact of heat shock proteins expression in patients with esophageal cancer: A meta-analysis.Yonsei Med J, 2015; 56(6): 1497–502
14. Lambot MA, Peny MO, Fayt I et al: Overexpression of 27-kDa heat shock protein relates to poor histological differentiation in human oesophageal squamous cell carcinoma. Histopathology, 2000; 36(4): 326–30
15. Chen XL, Zhou L, Yang J et al: Hepatocellular carcinoma-associated protein markers investigated by MALDI-TOF MS. Mol Med Rep, 2010; 3(4): 589–96
16. Meta E, Brullo C, Sidibe A et al: Design, synthesis and biological evaluation of new pyrazolyl-ureas and imidazopyrazolecarboxamides able to interfere with MAPK and PI3K upstream signaling involved in the angiogenesis. Eur J Med Chem, 2017; 133: 24–35
17. Liao RY, Zhang Y: Synthesis, crystal structures and anticancer activities of two naphthol derivatives. Lat Am J Pharm, 2015; 34(9): 1876–80
18. Fukushima C, Murakami A, Yoshitomi K et al: Comparative proteomic profiling in squamous cell carcinoma of the uterine cervix. Proteomics Clin Appl, 2011; 5(3–4):133–40
19. Feng YL, Yin YX, Ding J et al: Alpha-1-antitrypsin suppresses oxidative stress in preeclampsia by inhibiting the p38MAPK signaling pathway: An *in vivo* and *in vitro* study. PLoS One, 2017; 12(3): e0173711
20. Zhang P, Hong J, Yoon IN et al: Clostridium difficile toxin A induces reactive oxygen species production and p38MAPK activation to exert cellular toxicity in neuronal cells. J Microbiol Biotechnol, 2017; 27(6): 1163–70
21. Brichkina A, Bulavin DV: Cancer suppression by systemic inactivation of p38MAPK. Oncotarget, 2017; (8): 14275–76
22. Bonney EA: Mapping out p38MAPK. Am J Reprod Immunol, 2017 [Epub ahead of print]
23. Brichkina A, Nguyen NTM, Baskar R et al: Proline isomerisation as a novel regulatory mechanism for p38MAPK activation and functions. Cell Death Differ, 2016; 23(10): 1592–601
24. Shen Z, Xu L, Li J et al: Capilliposide C sensitizes esophageal squamous carcinoma cells to oxaliplatin by inducing apoptosis through the PI3K/Akt/mTOR pathway. Med Sci Monit, 2017; 23: 2096–103
25. Zemanova M, Vecka M, Petruželka L et al: Plasma phosphatidylcholines fatty acids in men with squamous cell esophageal cancer: Chemoradiotherapy improves abnormal profile. Med Sci Monit, 2016; 22: 4092–99
26. Guo Q, Wang HB, Li YH et al: Correlations of promoter methylation in WIF-1, RASSF1A, and CDH13 genes with the risk and prognosis of esophageal cancer. Med Sci Monit, 2016; 22: 2816–24

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