

ORIGINAL ARTICLE

Correlations of Moesin expression with the pathological stage, nerve infiltration, tumor location and pain severity in patients with pancreatic cancer

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Summary

Purpose: The study aimed to investigate the correlations of the expression of membrane-organizing extension spike protein (moesin) with the pathological stage, nerve infiltration, tumor location and pain severity in patients with pancreatic cancer (PC) and analyze its possible mechanism.

Methods: A total of 43 patients with pancreatic cancer receiving surgical resection in our hospital were enrolled, with the adjacent tissues as controls. Then, quantitative polymerase chain reaction (qPCR) and Western blotting were carried out to measure the expression level of the moesin messenger ribonucleic acid (mRNA) in PC tissues. The expression levels of matrix metalloproteinase-7 (MMP-7), tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6) and IL-10 (IL-10) in PC tissues were detected using enzyme-linked immunosorbent assay (ELISA) kit. The relationship between moesin and the pathological stage of patients was analyzed, followed by further analyses on the correlations of moesin with nerve infiltration, tumor location and pain severity of patients with PC.

Results: The results of qPCR and Western blotting demonstrated that the expression levels of the moesin mRNA and moesin in PC tissues were evidently higher than those in

adjacent tissues ($p < 0.01$). Based on ELISA, the expression levels of MMP-7, TNF- α and IL-6 ($p < 0.01$) were significantly higher, while the expression level of IL-10 ($p < 0.01$) was obviously lower in PC tissues compared with those in adjacent tissues. The expression of moesin was closely associated with the pathological stage of patients with PC ($p < 0.01$). The expression level of moesin in PC tissues in patients with nerve infiltration was significantly higher than that of those without nerve infiltration ($p < 0.01$). It was distinctly elevated in PC tissues of patients with tumors located in the tail of the pancreas in comparison with those with tumors located in the head of the pancreas ($p < 0.01$). The pain severity was correlated with the expression level of moesin in PC tissues ($p < 0.01$).

Conclusion: Moesin affects the progression of PC by activating MMP-7 and further promoting the release of TNF- α and IL-6 and decreasing the level of IL-10. The expression of moesin in PC tissues has close relations with the pathological stage of the disease, nerve infiltration, tumor location and pain severity.

Key words: moesin, pancreatic cancer, pathological stage, nerve infiltration, pain

Introduction

Pancreatic cancer (PC) is a common gastrointestinal malignant tumor characterized by high aggressiveness and rapid progression, and show increasing incidence rate in China in recent years [1]. PC is divided into head, body and tail carcinoma

based on different tumor locations. Since the signs and symptoms of pancreatic cancer at the early stage are not typical, its diagnosis is very difficult, and most patients with pancreatic cancer are already at the advanced stage when diagnosed [2].

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As for the treatment of PC, chemotherapy and surgery are applied. Chemotherapy mostly produces a poor effect, hence surgical resection of the tumor may be the only way to cure PC at present, but the rate of postoperative 5-year survival rate of patients is unfortunately low, which is mainly caused by metastasis of tumors before and after surgery [3]. PC is easy to invade to surrounding tissues at its early stage and after surgery, the incidence rates of infiltration and metastasis to important large blood vessels and nerve plexus are the highest, and nerve infiltration is a common mode of PC metastasis [4].

With the continuous development of proteomics and pathological typing of tumors, physicians have a better understanding of the pathogenesis and progression of pancreatic cancer. The membrane-organizing extension spike protein (moesin) is expressed in membrane protrusions and plays a crucial role in maintaining cytoskeleton and cell movement [5]. A lot of research evidence indicates that moesin is widely expressed in various tumor tissues and closely correlated with nerve infiltration and invasion of various tumors [6]. A study of Sanchez et al. [7] revealed that the expression level of moesin in estrogen receptor-negative cells is overtly higher than that in estrogen receptor-positive cells of breast cancer, which may be associated with the easy spread and metastasis of estrogen receptors. The research of Kobayashi et al. [8] found that the positive expression of moesin is associated with the clinical stage, lymphatic metastasis and pathological grade of oral squamous cell carcinoma. However, the correlations of moesin with the pathological stage, nerve infiltration, tumor location and pain severity of patients with PC are not analyzed in studies. Therefore, the expression of moesin in tumor tissues of patients with PC was analyzed in this study to further reveal the correlations of moesin with the pathological stage, nerve infiltration, tumor location and pain severity in patients with pancreatic cancer.

Methods

Subjects and grouping

This study got approvals from the Ethics Committees for Biomedical Research of our hospital. Besides, all enrolled patients signed the informed consent be-

fore surgery. Specimens were taken from patients with pancreatic cancer treated with surgical resection in our hospital from July 2015 to July 2017, which were definitely diagnosed by pathological biopsy after surgery. The pathological type of all specimens was pancreatic ductal adenocarcinoma. A total of 43 patients (28 males and 15 female), aged 43-78 years were enrolled in this study. Inclusion criteria: (1) Patients newly diagnosed, (2) accepting no treatment before surgery, (3) without other malignant tumors, (4) without obvious liver and kidney dysfunction, and (5) with obvious surgical indications. There were 28 males and 15 females, aged 43-78 years old. The adjacent tissues (over 3 cm away from the tumor free border) were taken from each group as controls, and the remaining PC tissues and adjacent tissues were stored in liquid nitrogen. Clinical pathological staging was performed according to the tumor-node-metastasis (TNM) criteria by the Union for International Cancer Control (UICC), and there were 6 patients in stage I, 12 patients in stage II, 10 patients in stage III, and 15 patients in stage T₄. Pathological data of all enrolled patients were kept for subsequent studies.

Detection of the moesin messenger ribonucleic acid (mRNA) expression level in pancreatic cancer tissues via quantitative polymerase chain reaction (qPCR)

Total RNA in tissues was extracted in strict accordance with the instructions of RNA extraction kits (TaKaRa, Tokyo, Japan): Pancreatic cancer tissues and adjacent tissues collected from each group of pancreatic cancer patients were taken out from liquid nitrogen. Then, tissues were added with TRIzol (Invitrogen, Carlsbad, CA, USA) at a ratio of 100 mg: 1 mL, pulverized using a manual homogenizer and centrifuged at 10000 rpm and 4°C for 10 min with a thermostatic centrifuge. After the supernatant was taken, the tissues were added with chloroform with the same volume of the supernatant, mixed via over 10 times of perversion and centrifuged at 12000 rpm and 4°C for 10 min. Thereafter, the supernatant was discarded, and 1 mL freshly prepared 75% ethanol was added, mixed by perversion, centrifuged at 12000 rpm and 4°C for 10 min. Next, the supernatant was discarded, and the remaining was dried naturally and dissolved with 50 µL diethylpyrocarbonate (DEPC) water to prepare into total RNA. The ratio of absorbance at 260 and 280 nm (A_{260}/A_{280}) and optical density (OD) value of RNA were determined. Total RNA was reversely transcribed using a reverse transcription kit (Invitrogen, Carlsbad, CA, USA), and the reaction system and conditions were set strictly according to the instructions. Then, amplification was carried out according to the instructions of qPCR kits (Invitrogen, Carlsbad, CA, USA): Conditions for qPCR was set with complementary deoxyribonucleic acid (cDNA) as the template. The amplification condi-

Table 1. Primer sequences

Gene	Forward primer sequence	Reverse primer sequence
moesin	5'-GTGCCAAGTTCTACCCTGAG-3'	5'-ATTCAGGACATCACTCAGCG-3'
GAPDH	5'-CCCATGTTTCGTCATGGGTGT-3'	5'-TGGTCATGAGTCCTTCCACGATA-3'

tions: pre-denaturation at 94°C for 2 min, denaturation at 94°C for 15 s, and annealing at 60°C for 30 s, 30 cycles in total. The primers were synthesized by Invitrogen, with sequences shown in Table 1. The calculation was performed using the formula $2^{-\Delta\Delta C_t}$, and the expression level of moesin in pancreatic cancer tissues and adjacent tissues was expressed as moesin/ glyceraldehyde-3-phosphate dehydrogenase (GAPDH).

Detection of related protein expression levels in pancreatic cancer tissues through Western blotting

Collected pancreatic cancer tissues and adjacent tissues were taken out from liquid ammonia, added with the pre-cooled radio immunoprecipitation assay (RIPA) lysis solution (Invitrogen, Carlsbad, CA, USA) at a ratio of 100 mg: 1 mL, and 1% protease and phosphatase inhibitors (Sigma, St. Louis, MO, USA), and homogenized with an ultrasonic homogenizer until there was no visible tissue fragments, followed by centrifugation at 10000 rpm and 4°C for 10 min using a thermostatic centrifuge. Next, the supernatant, namely, the total protein, was taken, quantified using a protein quantification kit (Millipore, Billerica, MA, USA) to prepare the sample system with an equal concentration, and boiled for use. After the spacer and separation gels were prepared based on the molecular weight of the protein, sample (20 μ L per well) was loaded for electrophoresis at constant voltage of 80 V. Then, the protein was transferred to a polyvinylidene fluoride (PVDF) membrane (Millipore, Billerica, MA, USA) via wet transfer method under constant current of 300 mA for 90 min. After the membrane transfer was completed, protein bands were blocked with freshly prepared 5% skim milk powder at room temperature for 1 h. Target bands were cut according to the molecular weight of target protein, and incubated with rabbit anti-moesin (Cell Signaling Technology, Danvers, MA, USA) and rabbit anti-GAPDH (Cell Signaling Technology, Danvers, MA, USA) at 4°C overnight. Then, bands were washed with Tris-buffered saline with Tween®20 (TBST) for 3 times (5 min/time), followed by incubation with corresponding horseradish peroxidase-conjugated secondary antibodies (Beyotime, Shanghai, China) at room temperature for 1 h and washing with TBST for 3 times (10 min/time). Next, illuminating solution (Beyotime, Shanghai, China) was freshly prepared, and protein bands were developed and exposed in a dark room. Lastly, the gray scale of bands was scanned using a scanner, and the relative expression level of moesin was calculated.

Detection of matrix metalloproteinase-7 (MMP-7) and inflammatory factor expression levels in pancreatic cancer tissues using enzyme-linked immunosorbent assay (ELISA)

The expression levels of corresponding proteins in pancreatic cancer tissues and adjacent tissues were measured using the MMP-7, tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6) and IL-10 ELISA kits (purchased from R&D system, Minneapolis, MN, USA) strictly following the relevant instructions. The absorbance values of the samples and standard substance were detected at 450 nm using a multimode reader (with blank wells as standard). CurveExpert 1.4 software was

employed to draw standard curves, and the concentration of corresponding sample was calculated.

Evaluation of nerve infiltration

Specimens of PC were collected from each group of patients and prepared into tissue sections. Sections of 5 sites of each group of patients were used. Detection of tumor cell infiltration in the nerve tract or on the perineurium in one of the tissue sections indicated positive, and the degree of nerve infiltration was classified by referring to the study of Huang et al. [9]: (1) 0 point for no infiltration of cancer cells to the peripheral nerves in all sections, (2) 1 point for 1-2 infiltration of cancer cells to the peripheral nerves in each section, (3) 2 points for 3-4 infiltration of cancer cells to the peripheral nerves in each section, and (4) 3 points for more than 4 infiltration of cancer cells to the peripheral nerves in each section.

Assessment of pain severity

After enrollment, each patient was subjected to pain scoring to evaluate the pain severity of patients. The scoring of pain severity was conducted according to the study of Lică et al. [10]: (1) 0 point for no pain, (2) 1 point for abdominal discomfort or tolerable pain alone, (3) 2 points for relatively severe pain that can be effectively alleviated by non-opioid drugs, and (4) 3 points for severe pain needing opioids for analgesia.

Statistics

All data in this study were expressed as mean \pm standard deviation and analyzed using SPSS 21.0 soft-

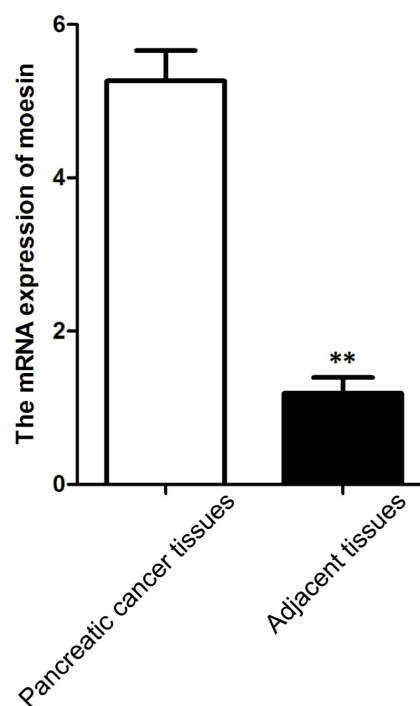


Figure 1. Expression level of the moesin mRNA in pancreatic cancer tissues measured via qPCR, the expression level of the moesin mRNA in pancreatic cancer tissues is obviously higher than that in adjacent tissues (** $p < 0.01$).

ware (SPSS Inc., Chicago, IL, USA). T-test was employed for comparisons between two groups, and χ^2 test was used for comparisons among multiple groups. For correlation analysis, linear regression analysis was applied, and correlation coefficients were calculated. $p < 0.05$ suggested that the difference was statistically significant.

Results

Expression levels of the moesin mRNA and moesin in pancreatic cancer tissues

The expression level of the moesin mRNA in cancer tissues of patients with pancreatic cancer was measured via qPCR, and adjacent tissues were used as controls. The results showed that the expression level of the moesin mRNA in cancer tissues of pancreatic cancer patients was significantly higher than that in adjacent tissues ($p < 0.01$) (Figure 1). Based on the determination of the expression level of moesin in cancer tissues of patients with pancreatic cancer using Western blotting, the expression level of moesin in cancer tissues of pancreatic cancer patients was overtly increased compared with that in adjacent tissues ($p < 0.01$) (Figure 2).

Correlations of moesin with pathological characteristics of patients

Clinical pathological data and general data of patients were recorded in detail, and the correlations of the expression level of moesin with the pathological stage, nerve infiltration, tumor loca-

tion and pain severity of patients were evaluated. The results are shown in Table 2. The expression of moesin was not associated with the age and gender of patients with pancreatic cancer ($p > 0.05$), but closely related to the pathological stage of PC patients ($p < 0.01$). The expression level of moesin in tumor tissues of PC patients with tumors located in the tail of the pancreas was distinctly higher than that of those with tumors located in the head of the pancreas ($p < 0.01$). In comparison with patients with no or mild nerve infiltration, moesin expression in tumor tissues of those with severer nerve infiltration was overtly elevated ($p < 0.01$). The severer the pain was, the higher the expression level of moesin in PC tissues would be ($p < 0.01$).

Correlations of the expression level of moesin with nerve infiltration and pain severity

Correlation analysis was employed to evaluate the correlations of moesin expression level with the nerve infiltration and pain severity in patients with PC. The results (shown in Figure 3) revealed that the expression of moesin was positively associated with nerve infiltration ($R^2 = 0.4291$, $p < 0.05$) and pain severity ($R^2 = 0.2743$, $p < 0.05$) in patients with PC.

Expression levels of inflammatory factors in cancer tissues of patients with PC

The expression levels of MMP-7, TNF- α , IL-6 and IL-10 in cancer tissues of PC patients were

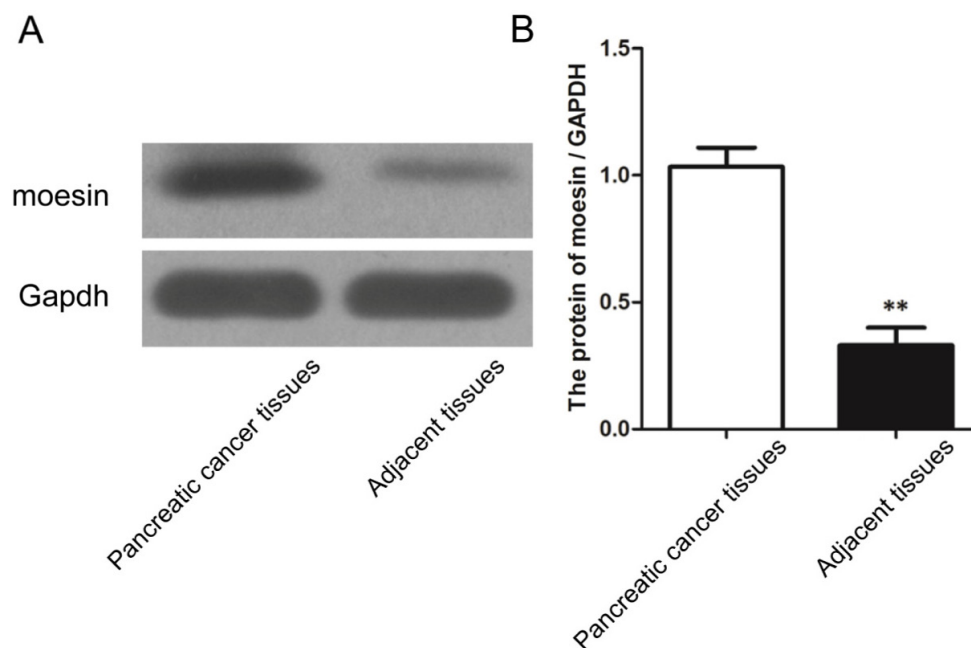


Figure 2. Determination of moesin expression level in pancreatic cancer tissues through Western blotting. **A:** Protein band diagram, **B:** Statistical diagram of moesin band, the expression level of moesin in pancreatic cancer tissues is evidently higher than that in adjacent tissues (** $p < 0.01$).

measured using ELISA kits. The expression levels of MMP-7, TNF- α and IL-6 in cancer tissues of patients with PC were obviously increased compared with those in adjacent tissues, while the expression level of IL-10 was evidently decreased compared with that in adjacent tissues ($p < 0.01$) (Figure 4).

Discussion

As one of the most aggressive malignant tumors of the digestive tract, PC has an extremely high incidence rate of tumor metastasis, nerve infiltration is the main method of tumor metastasis in PC, and the occurrence of nerve infiltration is

an important factor affecting the effect of surgical resection and prognosis of PC [11]. A study of Fujii-Nishimura et al. [12] found that among 204 patients with PC, over 70% of them suffer from nerve infiltration in the pancreas, and most infiltration is detected in peripheral nerve plexus of the superior mesenteric artery. In this study, the incidence rate of nerve infiltration in patients with PC was 69.8%, which is comparable to the incidence rate reported in the literature. Such a high incidence rate of nerve infiltration suggests that it should be taken into account in clinical diagnosis and surgical treatment of PC. During radical operation for PC, the peritoneal nerve should be dissected to

Table 2. Correlations of moesin with pathological characteristics of patients

Clinicopathologic features	n	Moesin expression level	p value
Age (years)			
≥ 50	11	2.895 \pm 0.852	>0.05
<50	32	2.914 \pm 0.936	
Gender			
Male	28	2.926 \pm 0.718	>0.05
Female	15	2.917 \pm 0.699	
Pathological stage			
Stage I-II	18	2.139 \pm 0.505	<0.05
Stage III-IV	25	2.952 \pm 0.337	
Nerve infiltration (grade)			
0-1	16	1.989 \pm 0.306	<0.05
2-3	27	2.825 \pm 0.192	
Tumor location (pancreas)			
Head	25	1.898 \pm 0.129	<0.05
Tail	18	3.081 \pm 0.523	
Severity of pain (grade)			
0-1	8	2.052 \pm 0.332	<0.05
2-3	35	2.963 \pm 0.225	

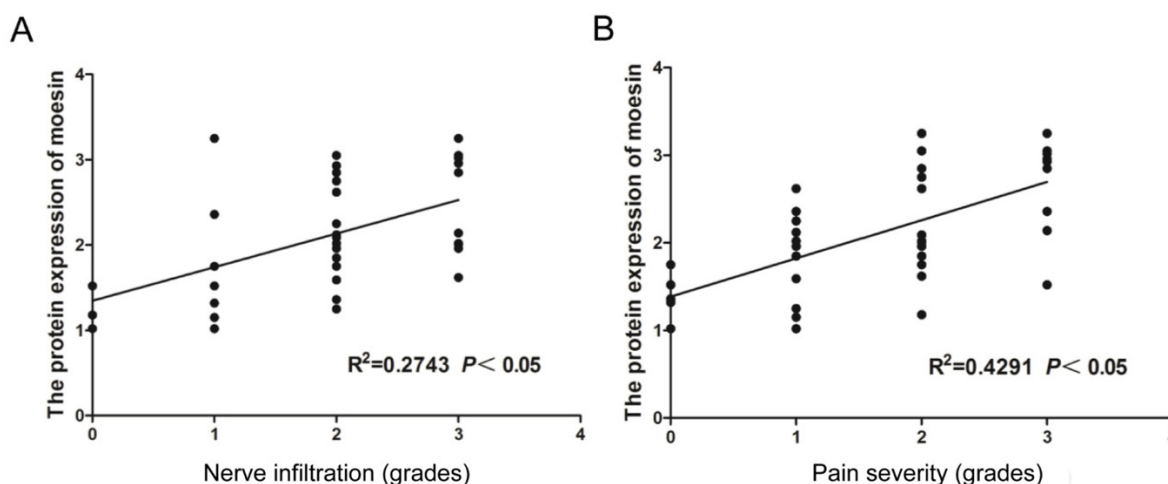


Figure 3. Correlation analysis. **A:** Relation between moesin and nerve infiltration. **B:** Association between moesin and pain severity.

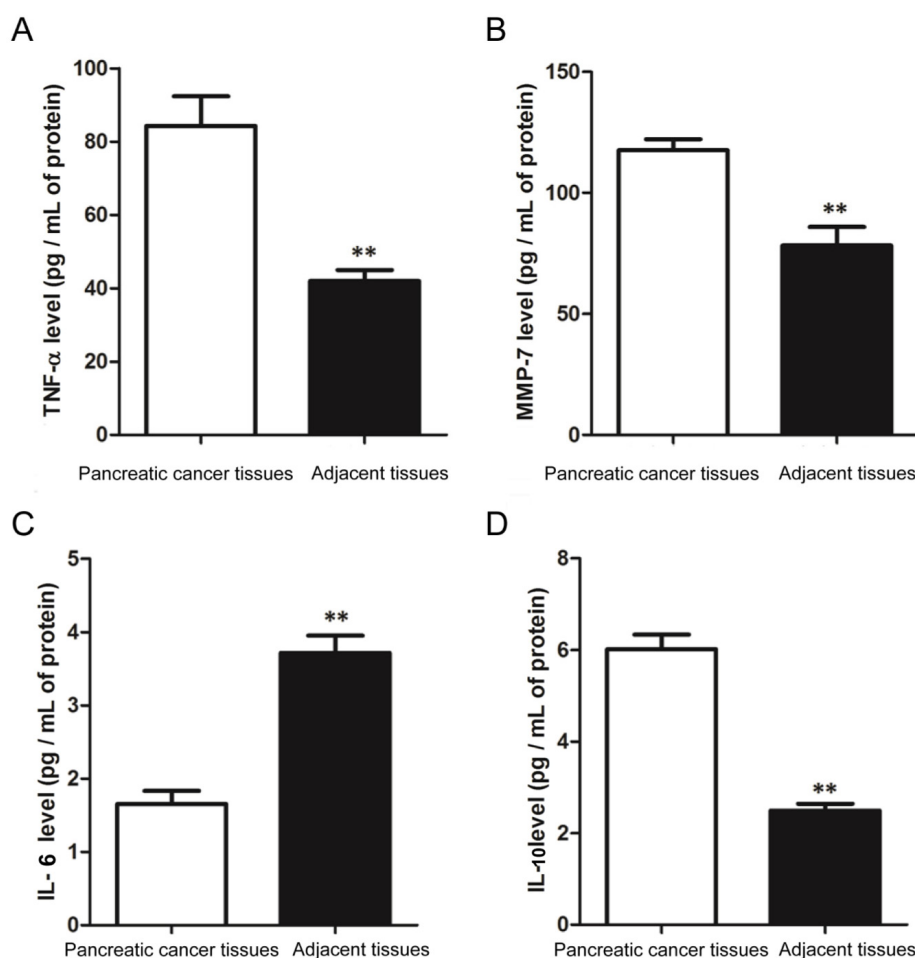


Figure 4. Detection of the expression levels of inflammatory factors using ELISA. **A:** Expression level of MMP-7, **B:** Expression level of TNF- α , **C:** Expression level of IL-6, **D:** Expression level of IL-10. Expression levels of MMP-7, TNF- α and IL-6 in pancreatic cancer tissues are obviously higher than those in adjacent tissues, while the expression level of IL-10 is evidently lower than that in adjacent tissues (** $p < 0.01$).

minimize the risk of recurrence and re-metastasis of PC. A common symptom of PC is abdominal and back pain. A study of Ben et al. [13] discovered that 30.7% of patients with PC go to hospital because of abdominal pain. Besides, a study of Zhu et al. [14] revealed that the incidence rate of abdominal and back pain in PC patients with nerve infiltration is significantly higher than that in those without nerve infiltration, and the pain caused by PC has a close relation to nerve infiltration. The mechanism of nerve infiltration of PC in causing pain remains unclear, but some researchers believe that the pain is induced by high-concentration biological factors produced in the surrounding environment after nerve infiltration of PC cells [15]. Moesin acts as a membrane-structured stretch spike protein, is involved in the invasion and infiltration of various tumors, and has high expression in various malignant tumor tissues [16].

In this study, the expression levels of moesin in 43 patients with PC were compared and analyzed, and it was found that the expression level

of moesin in PC tissues was evidently higher than that in adjacent tissues, and that was gradually increased with the progress in pathological stage of PC. A study of Chakraborty et al. [17] discovered that the expression level of moesin is related to the degree of aggression of liver cancer, the increased degree of malignant liver cancer leads to disorder of cell polarity, and the body compensates for the expression of moesin to maintain the normal morphology of cells. When pancreatic tumors occur in the tail of the pancreas, the expression level of moesin in cancer tissues is significantly higher than that in tumors located in the head of the pancreas, and the expression level of moesin is positively correlated with the degree of nerve infiltration and pain severity in patients with PC. The research of Beaty et al. [18] revealed that increased expression level of moesin causes a clear increase in the incidence rates of invasion and migration of breast cancer, and moesin is able to effectively increase the invasive ability of tumor cells to the wall membrane, leading to invasion and infiltration

of tumor cells. PC patients often have pain after nerve infiltration, and the pain is severer with the increase in the degree of infiltration. In this study, 83.6% of PC patients with nerve infiltration had severer pain.

MMP-7 is a kind of MMPs, which belongs to proteolytic enzymes and participates in the hydrolysis of fibrillar collagen, laminin, proteoglycan and gelatin. Moreover, it can effectually degrade the extracellular matrix and promote the tumor cell metastasis. Pathological conditions are capable of evidently increasing the content of MMP-7 in tissues and activating MMP-7, effectively promoting the metastasis and infiltration of tumor cells [19]. Increased expression level of moesin is able to clearly elevate the expression of MMP-7 in cells, promote the degradation of biological barriers such as collagen, and promote its expression in neovascularization to facilitate the metastasis of tumor cells. Furthermore, MMP-7 can further stimulate the release of inflammatory factors *in vivo*, leading to further damage and breakage of the matrix and

basement membrane [20]. It was discovered in this study that the expression level of MMP-7 in cancer tissues of patients with PC was overtly higher than that in adjacent tissues, and the expression levels of inflammatory factors TNF- α and IL-6 were evidently increased in cancer tissues of patients with PC, while the level of expression of anti-inflammatory factor IL-10 was significantly reduced.

Conclusions

In conclusion, moesin activates MMP-7, further promotes the release of TNF- α and IL-6 and lowers the level of IL-10, thus impacting the progression of PC. Besides, the expression of moesin is closely related to the pathological stage of the disease, nerve infiltration, tumor location and pain severity.

Conflict of interests

The authors declare no conflict of interests.

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