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The expression of TRPM7 in serum of patients with sepsis, its influences on inflammatory factors and prognosis, and its diagnostic value

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Abstract. – OBJECTIVE: This study aimed to investigate the expression of TRPM7 in the serum of patients with sepsis and its influences on inflammatory factors and prognosis.

PATIENTS AND METHODS: A prospective analysis was performed. 78 patients with sepsis were enrolled in the experimental group and treated from May 2015 to April 2017 in the Emergency Department of The Second Hospital of Dalian Medical University, and 75 healthy people were collected in the control group and received physical examinations during the same period. Real-time quantitative PCR was used to detect the relative expression of TRPM7, and sandwich enzyme-linked immunosorbent assay (ELISA) was applied to measure the serum expression levels of TNF-α, IL-6, and IL-10 in patients. Besides, the receiver operating characteristic (ROC) curve was drawn to analyze the diagnostic value of TRPM7.

RESULTS: The serum level of TRPM7 mRNA in the experimental group was higher than that in the control group ($p<0.05$). The serum levels of TNF-α, IL-6, and IL-10 in the experimental group were significantly higher than those in the control group ($p<0.05$). The optimal cut-off point value for the diagnosis of sepsis was 0.841; the specificity was 86%, and the sensitivity was 99%. Based on the survival data of the experimental group and the average expression level of TRPM7 which was 1.38, patients with a TRPM7 expression level less than 1.38 were divided into the low expression group, while those with a TRPM7 expression level equal or more than 1.38 were divided into the high expression group. The survival rate of the high expression group was significantly lower than that of the low expression group ($p<0.05$).

CONCLUSIONS: In summary, TRPM7, with high expression level in the serum of patients with sepsis is expected to be a potential prognostic indicator for sepsis.

Key Words

TRPM7, Sepsis, Inflammatory factors, Prognosis, Diagnostic value.

Introduction

Sepsis, a clinical syndrome, is characterized by an overwhelming inflammatory response that occurs after a severe infection[1]. Sepsis, the constellation of symptoms, occurs when an infection leads to systemic inflammatory responses, including fever, leukocytosis or leukopenia, decreased vascular resistance, frequently leading to hypotension (septic shock), organ failure (severe sepsis), and death[2]. Researches in the US found that the prevalence of pediatric severe sepsis has increased from 56 to 89 cases per 100,000 pediatric population[3,4]. Sepsis ranks among the top seven diseases by mortality[5]. Recently, exploration of the pathogenesis of sepsis and its sensitive markers has become a hot spot in clinical research.

TRPM7, a protein, binds an ion channel to an intrinsic kinase domain, allowing it to regulate cellular functions either by ion-conducting ions through the ion pore or by phosphorylating downstream proteins through its kinase domain[6]. In the past 15 years, TRPM7 was found to play an important role in peripheral tissues and cell lines. TRPM7 is involved in physiological and pathological processes, including embryonic development, organogenesis, cell proliferation and survival, and cell death[7]. TRPM7 has significant functions in ischemic and hypoxic brain damage and neuronal cell death[8]. One study has shown that TRPM7 plays a variety of functional roles in the biological processes of cancer cells, including survival, cell cycle progression, proliferation, growth, migration, and invasion, and the potential value of TRPM7 channel-kinase as a molecular biomarker and therapeutic target in human malignancies has been demonstrated[9]. Widely expressed in brain, kidney, liver and other organs, TRPM7 is involved in the development of various inflam-

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matory diseases such as myocardial fibers[10,11]. The relationship between TRPM7 and the synthesis and secretion of disease factors remains obscure. So far few studies have been made on TRPM7 in the serum of patients with sepsis. Therefore, the expression level of TRPM7 in the serum of patients with sepsis was observed, and the prognostic value and influences of TRPM7 on inflammatory factors and prognosis were explored in this study.

Patients and Methods

Patients

78 patients with sepsis who were treated in the Emergency Department of The Second Hospital of Dalian Medical University from May 2015 to April 2017 were enrolled in the experimental group, including 40 males and 38 females. They were 40 to 66 years old, with a mean age of (58.34 ±10.43) years. 75 people receiving the health examination during the same period were collected in the control group, including 36 males and 39 females. They were 40 to 67 years old, with an average age of (55.45 ± 13.95) years. Inclusion criteria: Patients in the experimental group were all with sepsis confirmed by pathological diagnosis, and subjects in the control group were all healthy according to the physical examination. Exclusion criteria: patients with other severe organ diseases, patients who did not cooperate with examinations, patients with cognitive impairment or communicative impairment. All subjects agreed to the serum collection for the experiment and cooperated with the medical staff to complete the relevant diagnosis and treatment. This study was carried out after the research contents were explained to the subjects and their families, and the informed consent form was signed. This study was approved by the Ethics Committee of the Second Hospital of Dalian Medical University.

Sample Collection

3 ml of venous blood was taken from each subject in the morning after 8 hours of fasting and was placed at room temperature for blood coagulation; then, the centrifugation was performed at 3000 r/min for 20 minutes. The supernatant was carefully collected to obtain serum, which was dispensed and stored at -80°C.

Main Instruments and Reagents

TRIzol Kit and DNase1 kit were from Sangon Biotech Co., Ltd. (Shanghai, China); cDNA Reverse Transcription Kit was purchased from TaKaRa Biotechnology Co., Ltd. (Dalian, China); UV spectrophotometer was provided by Beijing UP General Technology Co., Ltd. (Beijing, China); Fluorescence quantitative PCR kit was from Bio-Rad Laboratories, Inc. (Hercules, CA, USA); Real-time PCR detector (ABI7 500) was provided by Applied Biosystems Inc. (Waltham, MA, USA). TNF-α ELISA test kit (article number: BE45471) was provided by Tecan Trading Co., Ltd. (Shanghai, China); IL-6 ELISA test kit (article number: KIT10395) was manufactured by Beijing Lvyuan Bode Biotechnology Co., Ltd., (Beijing, China); IL-10 ELISA test kit (article number: BE45101) was from Tecan Trading Co., Ltd., (Shanghai, China).

Detection of TRPM7 Levels by Real-Time Quantitative Reverse Transcription-PCR (qRT-PCR)

The serum was taken out from a -80°C refrigerator and mixed with Trizol reagent for RNA extraction. Then 1 μl of total RNA was taken to measure the purity by an ultraviolet spectrophotometer according to the kit instructions. The reaction parameters of reverse transcription of RNA to cDNA: 16°C for 15 minutes, 42°C for 60 minutes, and 85°C for 5 minutes. Afterward, a PCR amplification system was configured according to the instructions to perform the amplification of cDNA, with U6 as the internal reference. The primer sequence is shown in Table I. The PCR reaction conditions: pre-denaturation at 95°C for 12 minutes, then 40 cycles of 95°C for 15 seconds, 65°C for 30 seconds. The relative expression of the gene was expressed by $2^{-\Delta CT}$, and ΔCT = Ct value of TRPM7 of each sample – Ct value of U6.

Determination of TNF-α, IL-6, and IL-10 Levels in Serum by Sandwich ELISA

ELISA was used to determine the concentrations of TNF-α, IL-6, IL-10 in the serum sample to be tested. The standard wells were set on the microplate and were added with 50 μl of the standard at the concentration of 0.15-1.8 μg/L respectively, then the blank wells and sample wells were set separately. 40 μl of the dilution and 10 μl of the sample were added to the sample well and mixed gently to dilute the sample by 5 times. Each reaction well was sealed with a sealing plate and incubated at 37°C for 30 minutes. Then, the sealing film was uncovered and the liquid in the reaction well was discarded. Following that, each well was filled with the diluted washing solution and dried after 30 seconds (this procedure referring to washing). After 5 times of such washing, each reaction well

Table I. Primer sequences of TRPM7.

Group	Forward primer	Reverse primer
TRPM7	5'-CTAGCCTTCAGCCACTGGAC-3'	5'-CCCTGAAAGGAAAAACGTCA-3'
U6	5'-ATTGGAACGATACAGAGAAGATT -3'	5'-GGAACGCTTCACGAATTTG -3'

was sealed again with a sealing plate and incubated at 37°C for 30 minutes. Next, after washing for 5 times, 50 µl of color-developing agent A and 50 µl of agent B were sequentially added in each well and mixed gently, then placed at 37°C in the dark for 15 minutes to perform the color-developing reaction. Finally, 50 µl of the stop solution was added to each well to terminate the reaction, and yellow color appeared in the wells. With the blank well as the zero-reference value, the optical density (OD) in each reaction well was measured using a spectrophotometer at a wavelength of 450 nm.

Statistical Analysis

The experimental data were statistically analyzed by the SPSS20.0 software package (IBM Corp, Armonk, NY, USA), and the experimental graphics were drawn using GraphPad Prism 7 software. The measurement data were expressed with mean ± standard deviation, and the *t*-test was used for analysis between the two groups. The count data were analyzed by the chi-square test. The receiver operating characteristic (ROC) curve was applied to determine the critical value of TRPM7. Survival analysis of the two groups was performed using the Kaplan-Meier method and compared using the Log-rank test. A statistical difference was recognized when $p<0.05$.

Results

General Information of the Two Groups

The two groups of subjects were comparable since they were not statistically different in terms of gender, age, weight, hypertension or not, heart rate, and body temperature ($p>0.05$). Specific general information is shown in Table II.

Table II. General information of patients in two groups [n (%), ($\overline{x}$ ± SD)].

Group	Experimental group (n=78)	Control group (n=75)	?²/t	p
Gender			0.026	0.823
Male	40 (51.28)	36 (48.00)		
Female	38 (48.72)	39 (52.00)		
Age (year)			0.011	0.916
≤55	37 (47.44)	34 (45.33)		
>55	41 (42.56)	41 (54.67)		
Weight (kg)			0.004	0.949
≤60	36 (46.15)	35 (46,67)		
>60	42 (53.85)	40 (53,33)		
Hypertension			0.781	0.377
Yes	18 (23.08)	13 (17.33)		
No	60 (76.92)	62 (82.67)		
Heart rate (beat/min)	113.66±23.19	109.73±22.65	1.060	0.291
Body temperature (°C)	36.76±1.36	37.16±1.41	1,786	0.0761
Severity of disease (case number, %)			—	—
Sepsis	25 (32.05)	—		
Severe sepsis	24 (30.77)	—	—	—
Septic shock	29 (37.18)	—		
Original infection (case number, %)			—	—
Respiratory tract infection	17 (21.79)	—		
Digestive tract infection	13 (16.67)	—		
Blood-borne infection	19 (24.36)	—		
Urinary tract infection	23 (29.49)	—		
Other	6 (0.69)	—		

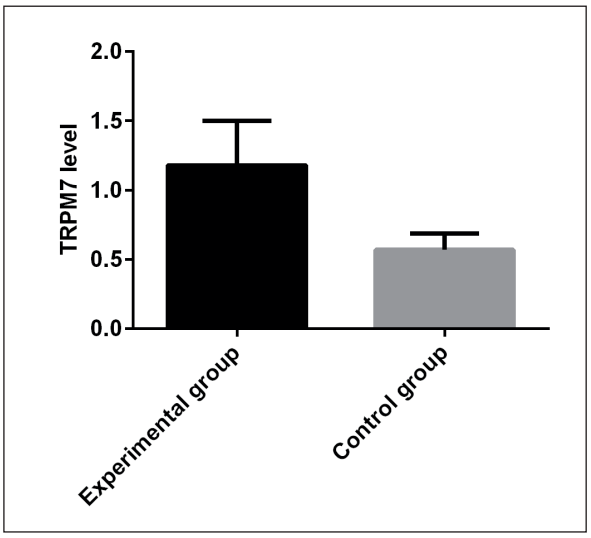

Figure 1. The relative expression of TRPM7 in two groups. According to the qRT-PCT detection, the experimental group had much higher TRPM7 expression than the control group, and the difference between the two groups was statistically significant (t=15.49, p<0.05).

Relative Expressions of TRPM7 in the Two Groups

The relative expression of TRPM7 in the experimental group was 1.38±0.32, much higher than that in the control group (0.57±0.12), and the difference between the two groups was statistically significant (t=15.49, p<0.05). Check Figure 1 for specific information.

Serum Levels of TNF-α, IL-6, IL-10 in the Two Groups

The serum levels of TNF-α, IL-6, and IL-10 in the experimental group were (235.36±31.76) ng/L, (116.78±21.76) ng/L, (58.78±14.67) ng/L, respectively, while those in the control group were (113.65±21.76) ng/L, (59.73±13.76) ng/L, and (49.76±13.28) ng/L, respectively. The serum levels of TNF-α, IL-6, and IL-10 in the experimental group were statistically much higher than those in the control group (p<0.05). See Table III for details.

The Diagnostic Value of TRPM7 in Patients with Sepsis

The results of the ROC curve showed that the AUG of serum TRPM7 for the diagnosis of sepsis was 0.952, the optimal cut-off point was 0.841, the specificity was 85.90%, and the sensitivity was 98.67%. See Figure 2 for details.

The Prognostic Value of TRPM7 in Patients with Sepsis

Based on the survival data of the experimental group and the average expression of TRPM7 which was 1.38, the experimental group were divided into two subgroups: 37 cases whose TRPM7 expression was less than 1.38 were in the low expression group, and 41 cases with a TRPM7 expression equal to or higher than 1.38 were in the high expression group. The end of the follow-up fell on April 2, 2018, up to when the survival rate of the high expression group was 39.02%, and the survival rate of the low expression group was 67.57%. Analysis on the K-M survival curve demonstrated that the survival rate of the high expression group was significantly lower than that of the low expression group, and the difference between the two groups was statistically significant (p<0.05). Turn to Figure 3 for specific information.

Discussion

Sepsis, a devastating disease, has an acute short-term mortality rate of approximately 70% in the case of septic shock[12]. Approximately 40-70% of the sepsis death cases are caused by severe sepsis and sepsis-induced multiple organ failure[13]. Uncontrolled inflammation induced by pathogens and subsequent immune disorders or immunosuppression is a potential mechanism of sepsis[14]. Immune regulation disorders play a key role in the development of sepsis. The initial immune response to sepsis is characterized by excessive producing and releasing of proinflam-

Table III. Serum levels of TNF-α, IL-6, IL-10 in the two groups ($\bar{x}$±SD, ng/L).

Group	TNF-α	IL-6	IL-10
Experimental group (n=78)	235.36±31.76	116.78±21.76	58.78±14.67
Control group (n=75)	113.65±21.76	59.73±13.76	49.76±13.28
t	27.55	19.30	4.116
p	<0.001	<0.001	<0.001

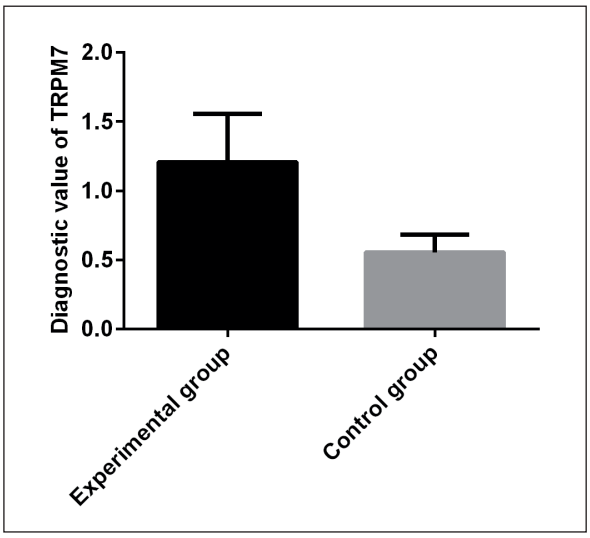

Figure 2. Diagnostic value of TRPM7 for sepsis. The results of the ROC curve showed that the AUG of serum TRPM7 for diagnosis of sepsis was 0.952, the optimal cut-off point was 0.841, the specificity was 85.90%, and the sensitivity was 98.67%.

matory mediators, leading to clinical symptoms such as fever, rapid heart rate and shortness of breath. Proinflammatory responses contribute to pathogen clearance and aggravation of immune damage[15]. The main pathogens of sepsis include bacteria, fungi, viruses and parasites, among which the Gram-negative bacteria are the most important[16]. Sepsis, a body infection occurring after serious burn, severe trauma, and major surgery, is aroused by complex factors, in which the concurrent immune promotion and immunosuppression will change as the development of the patient's condition[17]. The timely diagnosis of sepsis in the early stage is of great significance for controlling the risk of further deterioration, as well as for reducing its mortality rate.

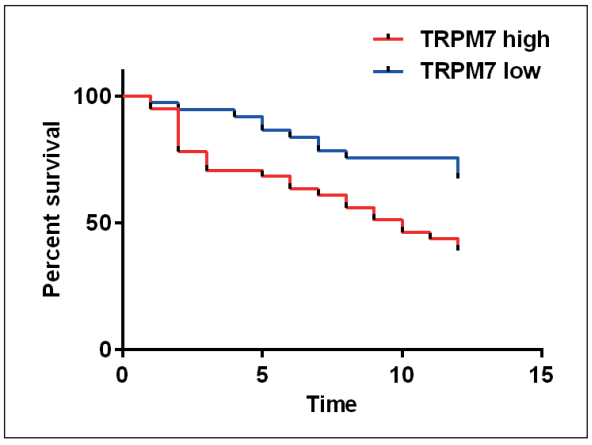

Figure 3. Prognostic value of TRPM7 for sepsis. Comparison of the survival rates between two subgroups of the experimental group demonstrated that the survival rate of the high expression group was statistically much lower than that of low expression group ($p<0.05$).

TRPM7 is a bifunctional protein with ion channels and kinase domains[18]. TRPM7 plays an important role in the magnesium homeostasis of the cellular system and early embryogenesis, it promotes calcium transport during cerebral ischemia and is an important participant in cancer development[19]. TRPM7 is also involved in other clinical pathological processes such as hypoxic neuronal death[20,21] and cardiac pathology[22,23]. It has been shown that TRPM7 kinase may be a promising antithrombotic target[24]. In Middelbeek's study of neuroblastoma, TRPM7 is part of a large cytoskeletal complex that affects the malignancy of tumor cells by regulating TRPM7[25]. In Sato-Kasai's study of mental illness, TRPM7 may be a new therapeutic target for schizophrenia[26]. In some studies, IL-6 is believed to inhibit the inward TRPM 7-like currents in primary cortical neurons and to regulate TRPM 7 currents through its α receptors[27]. So far, there are few studies on the expression and mechanism of TRPM7 in sepsis, which inspires this study to explore the expression of TRPM7 in sepsis serum and its influence on related inflammation factors and to analyze the diagnostic and prognostic values of TRPM7 in sepsis.

First, according to the qRT-PCR detection of the expression level of TRPM7 in the serum of patients with sepsis and in normal people, the TRPM7 of the experimental group was statistically much higher than that of the control group, indicating that TRPM7 is highly expressed in sepsis. It has been shown that the significant effect of TRPM7 deletion on macrophage response to LPS *in vitro* and in vivo sparks new thoughts for understanding the complex inflammatory processes. A detailed characterization of the role of TRPM7 in innate immune myeloid cells in LPS and, possibly, other TLR agonist-mediated inflammatory conditions could offer new potential therapeutic targets for modulating immune system activation during sepsis, bacterial infections and inflammatory diseases that chronically expose the organism to LPS and other TLR agonists[28]. Second, the ELISA method was applied to detect the levels of TNF-α, IL-6, and IL-10 in the serum of the two groups, and the result was that the experimental group had statistically much higher serum levels of TNF-α, IL-6,

and IL-10 than the control group, suggesting a higher TRPM7 level in patients with sepsis than in normal people, which may be related to inflammatory stimuli. TNF-α first appeared in the initiation phase of inflammation, which is the reason that it is also called the early inflammatory factor. From the study, inflammatory factors are closely related to infections such as fever, rapid heart rate, and organ dysfunction[29]. Finally, the prognostic and diagnostic values of TRPM7 in sepsis were analyzed by ROC curve which displayed that the AUG of serum TRPM7 for sepsis diagnosis was 0.952, the optimal cut-off point was 0.841, the specificity was 85.90%, and the sensitivity was 98.67%. The survival rate of patients was also compared between the high expression group and the low expression group. The result showed a statistically lower survival rate in the high expression group than in the low expression group, which indicates that TRPM7 has a marked value in the diagnosis of sepsis. With sepsis as the specific research object, this study explored the expression of TRPM7 and its diagnostic value in sepsis, suggesting certain significance for the diagnosis of sepsis. This study stands that monitoring the expression of TRPM7 in serum has a certain diagnostic value for the occurrence and development of sepsis, and can improve the accuracy of the diagnosis of sepsis, worthy of clinical promotion.

Conclusions

We observed that the high expression of TRPM7 can aggravate sepsis, so the monitoring of TRPM7 expression change in the serum can improve the accuracy of sepsis diagnosis. However, this study has some limitations as it failed to explore the biological function of TRPM7 in the serum of sepsis caused by a specific original infection, in the hope of enlarged sample size and further research on the role of TRPM7 in sepsis by other scholars.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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