Archives of Advances in Biosciences

Original Article:

The effects of serum separated from patients with sepsis on the expression of CXCR7 in mesenchymal stem cells (MSCs)

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Cite this article as: Ameri, F., Saghari, S., Atashi, A., Bitaraf, F. S., Raesi, R., Javan Sangani, N., & Haji Ghasem Kashani, M. (2025). Investigation of the effect of serum separated from patients with sepsis on the expression of CXCR7 in mesenchymal stem cells (MSCs). *Archives of Advances in Biosciences*, *16*(1), 1–10. https://doi.org/10.22037/aab.v16i1.49304

https://journals.sbmu.ac.ir/aab/article/view/49304

Article info:
Received: 26 Jul 2025
Accepted: 02 Sep 2025
Published: 21 Sep 2025

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Abstract

Introduction: Sepsis is a leading cause of death in intensive care unit (ICU) patients. This condition, in its advanced stage, leads to dysfunction of vital organs, resulting in the death of patients. Mesenchymal stem cells (MSCs) aid tissue regeneration by migrating to damaged areas, a process regulated by the CXCR7 gene. This study investigates the effect of serum from septic patients on the CXCR7 expression in MSCs.

Materials and Methods: The blood serum of 20 patients with sepsis was collected. The hUCB-MSCs were cultured under laboratory conditions (in vitro). Four groups of cells were treated with serum from patients and a control group was treated with serum from healthy volunteers. After 24 and 48 hours, the cells were trypsinized and RNA was extracted. cDNA was synthesized using a reverse transcription reaction and a specific kit. The expression level of this gene was determined using qRT-PCR.

Results: The results indicated that the expression of the CXCR7 gene in hUCB-MSCs treated with serum from sepsis patients significantly increased after 24 hours compared to the control group. Additionally, the expression level of this gene in the 48-hour treatment group showed a significant increase compared to the control groups and the 24-hour treatment group.

Conclusion: Exposure of hUCB-MSCs to septic patient serum led to a significant upregulation of CXCR7 compared with healthy serum (mean relative 2^−ΔΔCt fold-change: 24 h = 3.3-fold; 48 h = 19.3-fold; $P < 0.01$). These results are preliminary and warrant further functional and in vivo studies to confirm the biological and therapeutic implications of CXCR7 modulation in MSCs.

Keywords: Sepsis, CXCR7 gene, stem cells, mesenchymal stem cells (MSCs), umbilical cord, human

1. Introduction

Sepsis is a life-threatening condition characterized by dysregulated host responses to infection and remains one of the leading causes of mortality in intensive care units worldwide. Despite advances in supportive care, sepsis continues to result in multiple organ dysfunction and high global mortality rates. Current treatments focus primarily on infection control and maintaining organ function, but no specific therapy directly modulates the pathological immune responses that drive sepsis progression [1]. Diagnostic challenges further complicate management, as sepsis often presents with non-specific symptoms that overlap with other inflammatory conditions. Biomarkers such as procalcitonin (PCT), C-reactive protein (CRP), triggering receptor expressed on myeloid cells-1 (TREM-1), and CD64 expression in neutrophils have improved diagnostic accuracy, yet they have not translated into major therapeutic breakthroughs [2]. This urgent unmet need has stimulated interest in innovative strategies such as cell-based therapies. Mesenchymal stem cells (MSCs) have emerged as a promising therapeutic candidate for sepsis and other inflammatory diseases. MSCs are multipotent stromal cells that can be isolated from bone marrow, adipose tissue, or perinatal sources such as the umbilical cord. These cells exhibit immunomodulatory properties, promote tissue regeneration, and demonstrate the unique ability to home toward injured or inflamed tissues [3, 4]. In preclinical sepsis models, MSC therapy has been associated with improved survival, reduced systemic inflammation, and enhanced repair of organ damage [5]. The mechanisms underlying these benefits include paracrine secretion of cytokines and chemokines, modulation of immune cell activity, and homing to sites of injury. MSC homing is largely regulated by chemokine signaling pathways. Among these, the stromal-derived factor-1 (SDF-1 or CXCL12)/CXCR4 axis has been extensively studied and is considered the principal mechanism by which MSCs migrate to injured tissues [6, 7]. SDF-1 is widely expressed by stromal and endothelial cells, and its expression is strongly induced by proinflammatory cytokines such as TNF-α, IL-1β, and IL-6. Binding of CXCL12 to CXCR4 on MSCs activates intracellular signaling cascades (PI3K/AKT, MAPK/ERK) that enhance survival, chemotaxis, adhesion, and proliferation [8, 9]. However, MSC migration is not mediated exclusively by CXCR4, and emerging evidence highlights the importance of the second SDF-1 receptor, CXCR7.

CXCR7 (also known as ACKR3) is an atypical chemokine receptor located on chromosome 2q37. It binds CXCL12 with higher affinity than CXCR4 and also recognizes CXCL11 as a ligand [10]. Unlike CXCR4, CXCR7 signals predominantly through β-arrestin–mediated pathways rather than G-protein–coupled signaling. CXCR7 is expressed in multiple immune and stromal cell types, as well as in various cancers, where it regulates proliferation, survival, and metastatic behavior [11]. In MSCs, CXCR7 has been shown to fine-tune CXCR4 signaling, promote cell survival, and enhance adhesion to vascular endothelium [12, 13]. Importantly, the CXCL12/CXCR7 axis is increasingly recognized as a key regulator of MSC trafficking under inflammatory and hypoxic conditions [14]. Several experimental studies support the role of CXCR7 in MSC function. Overexpression of CXCR7 in MSCs enhances their migration and improves therapeutic efficacy in models of myocardial infarction and lung injury [15-17]. Conversely, silencing CXCR7 reduces MSC migration and impairs their reparative functions [14, 18]. In models of sepsis and acute lung injury, CXCR7 expression has been associated with improved cell engraftment and reduced tissue damage [19]. These findings indicate that CXCR7 is not simply a redundant receptor but a critical determinant of MSC behavior in inflammatory microenvironments. Despite these advances, there remain important knowledge gaps. Most studies of CXCR7 in MSCs rely on genetic manipulation or artificial overexpression systems, which may not fully reflect physiological regulation in human disease. Little is known about how the endogenous expression of CXCR7 in MSCs is modulated by the complex milieu of circulating factors present in sepsis. Septic serum contains a broad array of cytokines, chemokines, pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs) that may profoundly alter MSC biology. Understanding how this pathological environment affects CXCR7 expression could provide new insights into mechanisms of MSC homing and therapeutic action in sepsis. Therefore, the present study aimed to investigate the effect of serum from septic patients on CXCR7 expression in human umbilical cord blood–derived mesenchymal stem cells (hUCB-MSCs). Umbilical cord–derived MSCs are an attractive source for clinical applications due to their accessibility, high proliferative potential, and low immunogenicity [20]. By examining CXCR7 expression following exposure to septic serum, we sought to provide preliminary evidence on whether sepsis-associated circulating factors regulate this receptor. Our findings may contribute to a better understanding of

MSC biology in sepsis and inform future strategies to optimize MSC-based therapies for this devastating condition.

2. Materials and Methods

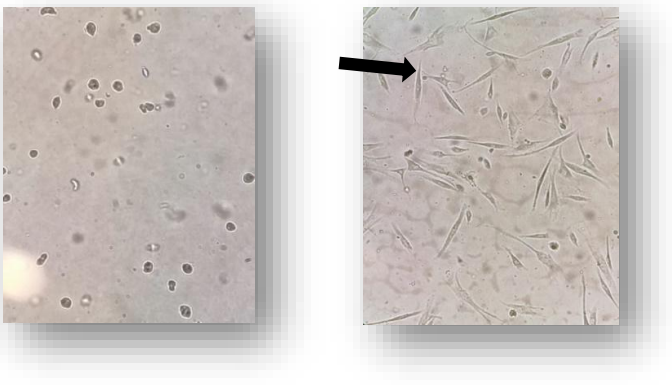
The blood serum of 20 patients with sepsis was collected. Consent, 5 cc more than the required amount for the hospital laboratory, was taken separately from it. The patients' samples were taken to the hospital laboratory to count white cells, PCT, CRP, sTREM-1, and CD64 biomarkers, and after confirming the disease, the type of pathogen was determined by diagnostic kits. After that, the sera collected for this study were transferred to the laboratory of Shahrood University of Medical Sciences. The cells were cultured in DMEM containing 10% FBS and cell passage was performed every 2 days [21]. After centrifugation of trypsinized cells in passages 3 or 4, cells were counted using trypan blue dye and the following method [22].

Number of cells per milliliter = 10^4 × 2 (dilution) × average of 4 counts

Cells from each T25 flask that reached over 80% confluency were split into four wells of a 6-well plate and supplemented with complete culture medium. After 24 hours, once the cells adhered to the plate, they were washed with PBS. Subsequently, 2 mL of DMEM, 50 µL of FBS, and 500 µL of sample sera were added to each well. Patient sera were randomly mixed with various microorganisms and categorized into four groups. Serum from a healthy volunteer served as the control group. Each group was assigned to four wells of the plate. RNA was extracted from the cells in two wells after 24 hours and from the other two wells after 48 hours of serum treatment. In this study, the 2^(-ΔΔCt) method, first introduced by Livak and Schmittgen in 2001 [22], was used to determine relative gene expression. This method analyzes relative changes in gene expression from real-time PCR data. Primers were designed using NCBI Primer-BLAST and AlleleID software. Relative gene expression was calculated using the 2^(-ΔΔCt) method. Serum samples from 20 septic patients were included as independent biological replicates. For each patient-derived serum, mesenchymal stem cells (MSCs) were cultured in four wells; RNA was extracted from two wells after 24 hours and from two wells after 48 hours. qRT-PCR reactions were performed in triplicate (technical replicates) for each sample, and experiments were independently repeated twice. Data are presented as mean ± SEM. Normality was assessed using the Shapiro-Wilk test. One-way ANOVA was used to compare groups, followed by Tukey's post-hoc test for pairwise comparisons. Exact p-values are reported in the Results section and tables, with significance set at $\alpha = 0.05$. Statistical analyses were conducted using GraphPad Prism version 6.

3. Results

People who had suspicious clinical symptoms such as chills, body temperature higher than 38 or lower than 36 degrees Celsius, rapid breathing (more than 20 times per minute), increased heart rate (more than 90 times per minute), were investigated. To confirm the disease of sepsis, the pathogen type detection test was performed on urine culture samples or respiratory secretions, and if there were wound secretions from the patients. Investigating the morphology of umbilical cord mesenchymal stem cells: Umbilical cord MSCs are spherical before attachment to the bottom of the flask, and after attachment, they appear spindle-shaped and fibroblast-like [Figure 1].



B A

Figure 1. Morphology of human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs). (A) Freshly plated hUCB-MSCs with round morphology before attachment. (B) Spindle-shaped fibroblast-like morphology after adherence and spreading at passage 3. Images were captured with an inverted phase-contrast microscope at 200× magnification. Scale bar = 100 µm. Images are representative of cultures used for experiments.

Verification of the identity of umbilical cord mesenchymal stem cells by flow cytometry and their staining: Flow cytometry results showed that human umbilical cord MSCs expressed CD73, CD166, and CD105 markers and were negative for CD34 and CD45 markers. The histogram shows a clearer picture of the expression of the markers [Figure 2].

Adipogenic staining of MSC differentiation showed that these cells stained positively with Sudan III and fat vacuoles were formed in the differentiated cells. Also, osteogenic differentiation staining of MSCs has a positive alizarin red color and indicates the mineralization of differentiated osteogenic cells [Figure 3].

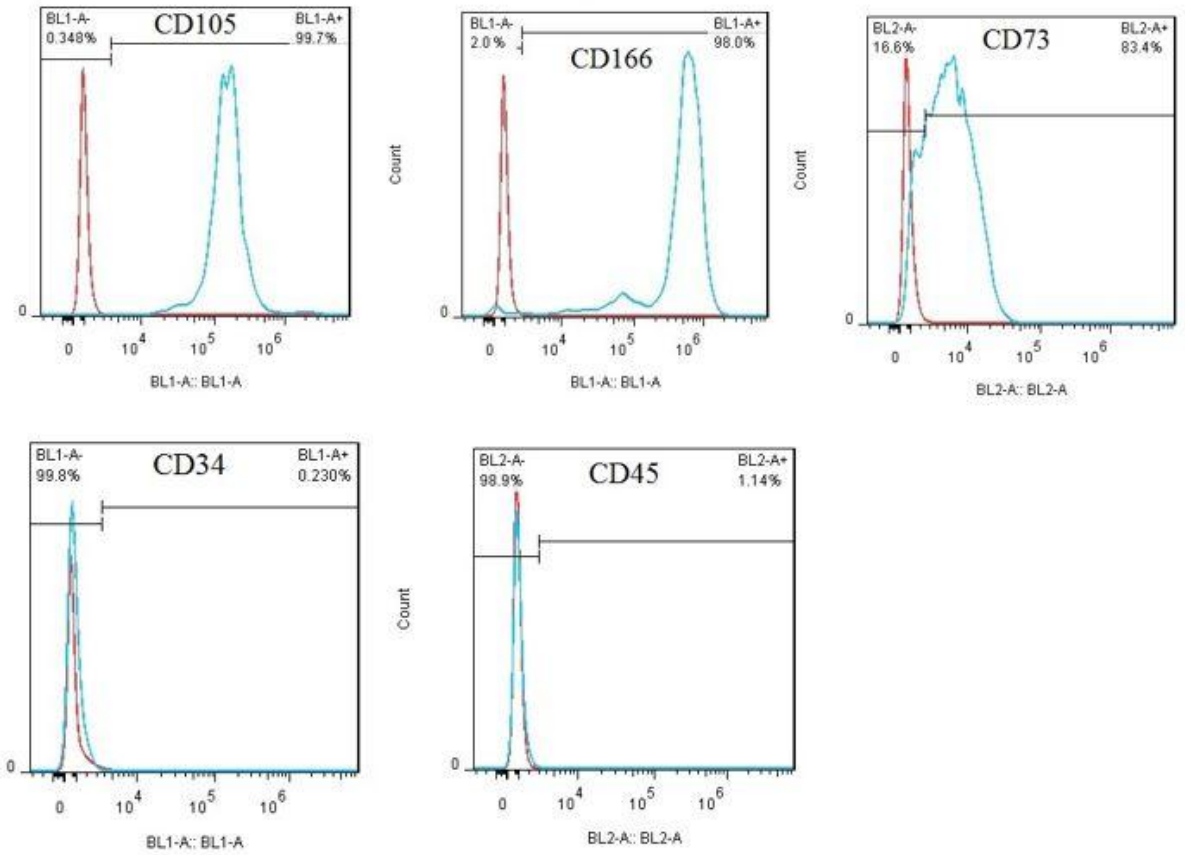


Figure 2. Flow cytometric immunophenotyping of hUCB-MSCs. Histogram plots showing high expression of MSC markers CD73 (97.2%), CD166 (95.6%), and CD105 (96.4%) and absence of hematopoietic markers CD34 (2.1%) and CD45 (1.7%). Gating was based on forward/side scatter and isotype controls. Data shown are representative of three independent cultures at passage 3.

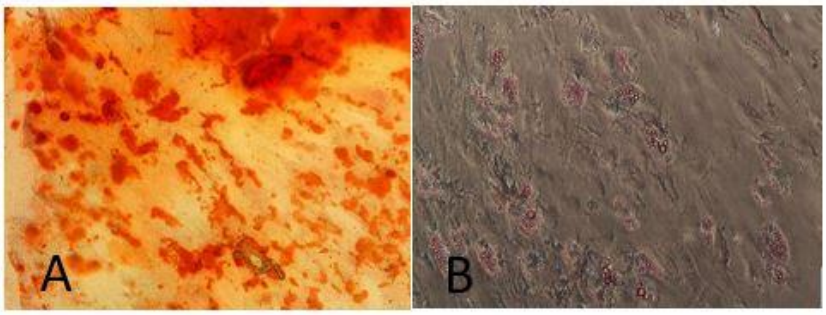


Figure 3. Differentiation potential of hUCB-MSCs. (A) Adipogenic differentiation confirmed by Sudan III staining, showing red-stained lipid droplets. (B) Osteogenic differentiation confirmed by Alizarin Red staining of calcium deposits. Experiments performed with passage 3 cells; images representative of three independent experiments. Scale bar = 100 µm.

RNA extraction and quality control results: To investigate the effect of sepsis patient serum on CXCR7 gene expression in umbilical cord mesenchymal stem cells, we treated MSCs with a culture medium containing 10% FBS and patient serum in a ratio of 4:1. After two periods of 24 and 48 hours, RNAs were extracted. To control the quality of the extracted RNAs, their amount was measured by absorption at a wavelength of 260 nm in a spectrophotometer, and to determine their purity, the ratio of absorption at a wavelength of 260 nm to a wavelength of 280 nm was measured.

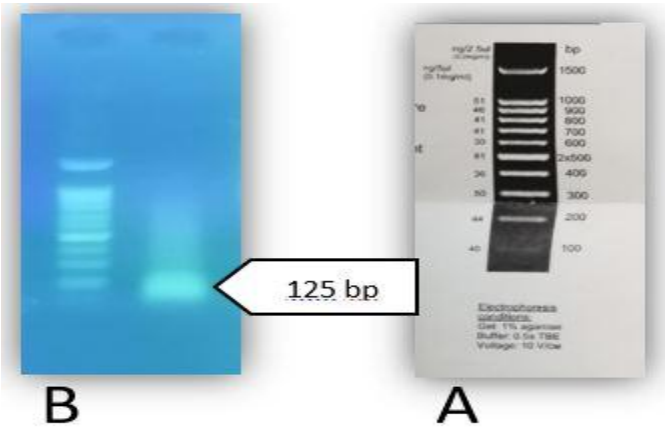


Figure 4. PCR product of HPRT internal control gene. Agarose gel electrophoresis showing a clear band at the expected size (125 bp). Lane 1: DNA ladder (100 bp ladder); Lane 2: HPRT amplicon. PCR products were obtained as described in Methods. Gel is representative of two independent PCR runs.

qRT-PCR results: After extracting and checking the quality control of RNAs, cDNA synthesis of the CXCR7 gene (main gene) and HPRT gene (as internal control) was produced using the cDNA synthesis kit from the extracted RNAs [Figure 4]. Then, the qRT-PCR reaction was repeated twice using the Biorad thermal cycler, and the results are as follows (Tables 1 & 2).

Table 1. Results of the first qRT-PCR

Group	HPRT	CXCR7	Fold change	Mean fold change
1/24	30/91	29/06	4/02782	3/294734
2/24	31/4	29/68	3/68075	
3/24	30/76	30/06	1/81503	
4/24	31/4	29/69	3/65532	
c/24	28/36	28/52	——	
1/48	29/82	28/42	29/2426	19/81806
2/48	30/15	29/66	16/2233	
3/48	31/17	30/08	23/1028	
4/48	28/55	28/6	10/7034	
c/48	26/61	30/08	——	

Table 2. Results of the second qRT-PCR

Group	HPRT	CXCR7	Fold change	Mean fold change
1/24	28/38	28/18	2/25012	2/119649
2/24	28/72	28/26	2/69447	
3/24	26/07	26/36	1/60214	
4/24	26/41	26/43	1/93187	
c/24	27/48	28/45	——	
1/48	28/66	27/86	2/01391	1/123105
2/48	26/15	26/84	0/71698	
3/48	26/94	27/53	0/76844	
4/48	27/93	28/19	0/99309	
c/48	27/93	28/14	——	

The results of CXCR7 gene expression by real time PCR device

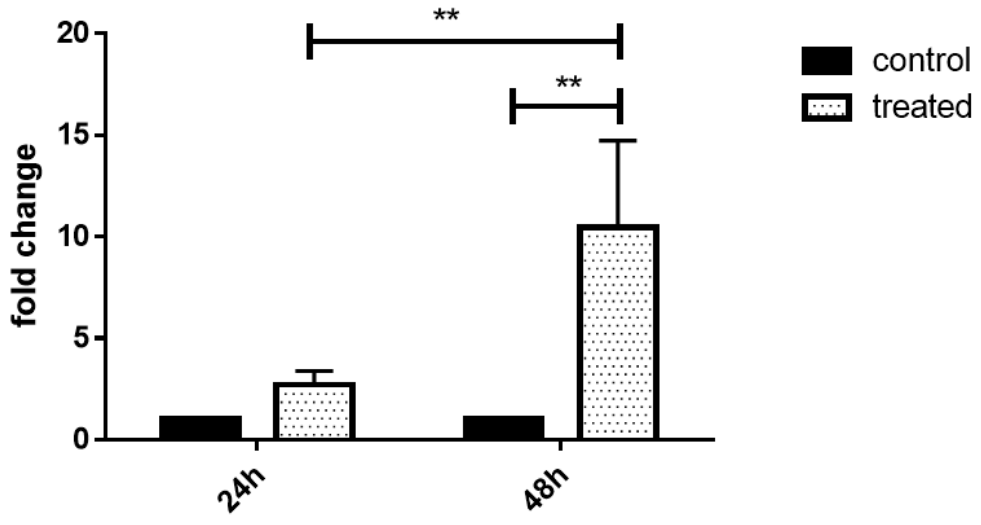


Figure 5. Relative expression of CXCR7 in hUCB-MSCs after exposure to septic patient serum. Bar graph shows mean relative expression (2^−ΔΔCt) compared with healthy serum controls at 24 h and 48 h. Expression increased

significantly at 24 h (3.3-fold vs control, $P < 0.01$) and further at 48 h (19.3-fold vs control, $P < 0.01$; also significantly higher than 24 h, $P < 0.01$). Data represent mean ± SEM from two independent qRT-PCR runs (Tables 1 and 2), each performed in triplicate technical replicates. Statistical analysis: one-way ANOVA with Tukey's post-hoc test (GraphPad Prism v6).

According to the Figure 5, the expression level of the CXCR7 gene in the groups treated with patient serum has increased compared to the group treated with healthy serum. This increase is significant in the 48-hour treatment groups compared to the control group and compared to the 24-hour groups.

4. Discussion

The rise of sepsis, affecting about 300 million people per year, especially in developing countries, has made it one of the major concerns in global health [23]. This disease, identified as a leading cause of death in hospitals, is triggered by the body's immune system response to infection. Almost any type of microbial infection in any part of the body can lead to sepsis, but research shows that bacterial infections are the most common cause. Treating sepsis with antimicrobials sometimes faces challenges due to the resistance of many microbes to existing drugs. Without proper treatment, the toxins produced by the pathogen can enter the bloodstream, initiating inflammatory and anti-inflammatory responses that damage vital organs such as the heart, brain, lungs, liver, and kidneys. In cases where sepsis progresses to septic shock, the blood supply to tissues and organs is compromised, leading to organ failure and death [24, 25]. While various microbial factors can cause sepsis, the most deadly type is sepsis caused by Gram-negative bacteria, particularly Escherichia coli [26]. This disease begins with the activity of macrophages. PAMPs such as lipopolysaccharide or pathogenic DNA, or DAMPs such as HMGB1, bind to the PRRs of macrophages and activate them. After that, cytokines that initiate pro-inflammatory cascades such as TNF-α, IL-1β, IL-6, IL-8, etc., are released, and then other pro-inflammatory cells such as monocytes and neutrophils are activated [27]. Among the pro-inflammatory responses that occur in the patient's body, we can mention the accumulation of fluids in the intercellular space, the destruction of damaged tissue, the fight against microorganisms at the site of inflammation, intravascular coagulation, and the disruption of body homeostasis. These reactions play an important role in limiting pathogen activity. However, if the inflammatory responses persist and there is no therapeutic intervention, factors that reduce inflammation such as regulatory T cells are activated. These factors can suppress the body's immunity by inhibiting the activity of pro-inflammatory cells. Also, with the increase in intravascular coagulation, the blood supply to the organs is disturbed, and the disease enters the stage of septic shock. At this stage, multiple organ dysfunction syndrome (MODS) occurs, which increases the risk of death due to the lack of definitive treatment [27, 28].

The observed upregulation of CXCR7 in hUCB-MSCs exposed to septic serum suggests potential enhancements in MSC functionality within inflammatory environments. CXCR7 is known to fine-tune CXCL12 signaling, often in concert with CXCR4, to promote MSC migration and homing to sites of injury or inflammation [13, 14]. Increased CXCR7 expression could amplify chemotactic responses to CXCL12 gradients, which are elevated in septic tissues due to proinflammatory cytokines like TNF-α and IL-1β, thereby facilitating more efficient MSC recruitment and engraftment [6, 15]. In terms of immunomodulation, CXCR7 may contribute to MSC-mediated suppression of excessive inflammation by modulating β-arrestin pathways, which influence cytokine secretion and immune cell interactions; for instance, studies in arthritis and lung injury models have shown that CXCR7-overexpressing MSCs exhibit heightened anti-inflammatory effects, including reduced proinflammatory cytokine production and enhanced regulatory T-cell induction [14, 19]. Regarding tissue repair, upregulated CXCR7 has been associated with improved MSC survival under hypoxic or stressful conditions, as well as enhanced paracrine signaling that promotes angiogenesis and extracellular matrix remodeling, leading to better outcomes in models of myocardial infarction and pulmonary hypertension [15-17]. While these mechanisms align with our findings of time-dependent CXCR7 induction (3.3-fold at 24 h and 19.3-fold at 48 h), they remain speculative in the context of sepsis and require direct functional validation through assays such as transwell migration, cytokine profiling, and in vivo sepsis models to confirm therapeutic relevance. Due to the lack of definitive treatment for severe sepsis and septic shock, the use of stem cells is considered a promising new approach to treat this disease, and mesenchymal stem cells are a suitable option for this method. After entering the body, these cells are activated by LPS or TNF-α and modulate macrophage activity by releasing prostaglandin E2. Prostaglandin E2 induces macrophages to produce and release the anti-inflammatory cytokine IL-10 through EP2 and EP4 receptors. In addition, these cells release the

antimicrobial peptide LL-37 in response to bacterial stimulation such as E. coli, and by preventing the activity of the endotoxin of bacteria, they reduce inflammation and pathogen effects in the body [29]. They also reduce cellular apoptosis [30]. There are different sources of MSCs in the adult human body and the fetus, among which the most important and useful sources are the bone marrow and fat in the adult human, and the amniotic fluid, placenta, and umbilical cord in the fetus.

5. Conclusion

Exposure of hUCB-MSCs to septic patient serum resulted in significant upregulation of CXCR7 expression. This observation suggests that circulating factors in sepsis can modulate chemokine receptor expression in MSCs, potentially altering their migratory and survival properties. However, because our study is limited to transcriptional analysis in vitro, further work—including functional migration/adhesion assays, manipulation of CXCR7 expression, cytokine profiling of sera, and in vivo homing studies—is required to establish the mechanistic and therapeutic relevance of CXCR7 modulation in MSC-based strategies for sepsis.

Ethical Considerations

Compliance with ethical guidelines

Before data collection, written informed consent was obtained from all the patients participating in the research, and the patients entered the study voluntarily. All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards. Considering that the data were extracted from archived medical records, there was no need for additional informed consent from the patients. This article reports the results of a research project approved by Damghan University with the ethics code IR.SHMU.REC.1398.038.

Funding

This research was conducted with the financial support of Damghan University of Medical Sciences.

Author's contributions

The authors equally contributed to preparing this article.

Conflict of interest

The authors have no conflict of interest to declare.

Acknowledgments

We would like to thank the Research Vice-Chancellor of Damghan University, the patients participating in the research, and all the individuals who contributed to the completion of this research.

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