Human peripheral blood CD34+ cells attenuate oleic acid–induced acute lung injury in rats

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Abstract

Background aims. Adult stem cell–based therapy is a promising novel approach for treatment of acute lung injury (ALI). In this study, we evaluated the therapeutic effect of isolated human peripheral blood CD34+ progenitor cells in an ALI rat model, induced by oleic acid (OA) injection. Methods. Seventy-five adult female rats were used in this study. Group A, control without treatment, and group B, control injected with phosphate-buffered saline, comprised 15 rats each; the remaining 45 rats were injected with OA to induce ALI and were further subdivided into 3 groups: group C (ALI group, 15 rats), group D (ALI and fibroblast group, 15 rats) and group E (ALI and CD34+ cell group, 15 rats). Results. CD34+ cells transplantation in rats with OA-induced lung injury improves the arterial PaO2 and wet/dry ratio, reduces infiltration of inflammatory cells and decreases lung vascular permeability as determined by reduced intra-alveolar and interstitial patchy congestion and hemorrhage as well as decreased interstitial edema. Additionally, lung inflammation determined by expression of the pro-inflammatory mediators intercellular adhesion molecule 1 and tumor necrosis factor-α was attenuated in CD34+ cell–treated rats at 6, 24 and 48 h post-OA challenge compared with non-treated rats. Moreover, the expression of anti-inflammatory molecule interleukin-10 was up-regulated in the lung of OA-induced ALI rats after administration of CD34+ cells. The important finding was that human TNF-α-induced protein 6 (TSG-6) gene expression was significantly up-regulated in rats treated with CD34+ cells. Conclusions. The freshly isolated human peripheral blood–derived CD34+ cells may be used as an important source of stem cells that improve ALI. The anti-inflammatory properties of CD34+ cells in the lung are explained, at least in part, by activation of CD34+ cells to express TSG-6.

Key Words: acute lung injury, CD34+ ve, ICAM-1, IL-10, TNF-α, oleic acid, TSG-6

Introduction

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are life-threatening conditions of acute respiratory failure that carry a 40% mortality in critically ill patients [1]. ALI/ARDS is initiated by direct lung injury or systemic inflammatory processes. Cellular characteristics of ALI include loss of alveolar-capillary membrane integrity, excessive trans-epithelial neutrophil migration and release of pro-inflammatory cytotoxic mediators [2].

Different animal models of experimental lung injury have been used to study ALI; most are based on reproducing known risk factors for ARDS, such as the administration of intratracheal lipopolysaccharide (LPS), intratracheal hydrogen chloride, repeated saline lavage, endotoxin infusion and intravenous injection of oleic acid (OA) [3]. OA-induced ALI is a well characterized and clinically relevant model of ALI/ARDS. In particular, it constitutes an excellent model of fat embolism syndrome–induced ALI, given that OA is a major component of the marrow-derived fat emboli released into the circulation after traumatic bone injury. The ALI produced by OA is relatively transient and resolves over 3 days [4,5].

No specific therapy for ALI/ARDS has been beneficial; instead, the patient is managed in terms of respiratory, circulatory and nutritional support. Recently, several new treatments, including inhaled nitrous oxide, instilled surfactant and interleukin
(IL)-1 receptor antagonist have been attempted with ALI/ARDS and related disorders, but they have achieved little improvement in patient survival, and the mortality rate remains as high as 40% [6,7]. Thus, novel therapeutic strategies are needed to improve the outcome of this devastating disease. Recently, mesenchymal stem cells (MSCs) are shown to be protective in animal models of ALI induced by oleic acid (OA) [4], LPS [8] and live bacteria [9–11]. Other studies have suggested that human adult stem cells might have therapeutic effects on ALI/ARDS [12,13].

CD34 is a member of a family of single-pass transmembrane sialomucin proteins [14]. Cells expressing CD34 (CD34+ cells) are normally found in the umbilical cord blood and bone marrow as hematopoietic stem cells (HSCs), endothelial progenitor cells and activated endothelial cells of blood vessels [15]. A subpopulation of CD34+ mononuclear blood cells isolated from human peripheral blood induces angiogenesis [15]. Human CD34+ progenitor cells isolated from bone marrow, peripheral blood and cord blood have been tested in many preclinical models of ischemic vascular diseases. These cells are efficient to promote angiogenesis and provide beneficial effects on myocardial infarction [16], peripheral ischemia [17] and ischemic stroke [18]. More important, some clinical studies also confirmed the beneficial effects of human CD34+ progenitor cells on coronary heart and peripheral vascular diseases [19]. Injection of CD34+ HSCs has been clinically applied to treat other non-vascular diseases including spinal cord injury [20] and liver cirrhosis [21]. However, little is known about the effects of human CD34+ progenitor cells isolated from peripheral blood on ALI induced by OA. Only 1 recent published study has reported protective effects of umbilical cord–derived CD34+ cells on ALI induced by LPS challenge [22].

We hypothesized that intravenous injection of CD34+ cells could attenuate ALI induced by OA injection in a rat model, and, if so, the protective mechanism may be mediated by anti-inflammatory effects. We also demonstrated whether the anti-inflammatory properties of CD34+ cells were explained, at least in part, by activation of CD34+cells to express the anti-inflammatory factor TNF-α-induced protein 6 (TSG-6).

Methods
This study was performed in 3 collaborating laboratories in Egypt: the Clinical Chemistry and Stem Cell Research Laboratory, Medical Biochemistry and Molecular Biology Department, Faculty of Medicine, Zagazig University; the Molecular Biology and Biotechnology Research Unit, Animal Wealth Development Department, Genetics and Genetic Engineering, Faculty of Veterinary Medicine, Zagazig University; and the Biotechnology Laboratory, Faculty of Veterinary Medicine, Kafrelsheikh University.

Animal preparation
Seventy-five healthy adult female rats of matched weight (200 ± 15 g) were used in this study. The rats were housed under standard conditions of light-dark cycles with free access to food and tap water under controlled temperature (28–30°C). They were observed in this environment for 7 days before commencing treatment ensuring adequate adaptation. Animal housing conditions and all experimental procedures conformed to institutional guidelines and were in accordance with the National Institutes of Health guidelines on animal care.

Isolation of CD34+ cells from human peripheral blood
Human peripheral blood (1500 mL) was obtained from 15 healthy male volunteers aged 33.7 ± 1.5 years after strenuous physical exercise according to To et al. [23]. One hundred milliliters of blood was collected from each volunteer. Informed consent regarding the experimental use of the blood from the volunteers was obtained.

From the peripheral blood, the mononuclear cells (MNCs) were obtained by centrifugation over Ficoll-Paque (lymphocyte separation medium 1.077, Lonza Bioproducts). After washing in phosphate-buffered saline (PBS), ~4.5 × 10^8 MNCs were left from each 200 mL of blood. CD34+ cells were isolated from MNCs by the MACS CD34 progenitor isolation kit using immunomagnetic beads (CD34 MicroBead Kit, Miltenyi Biotec) as described previously [24]. The purified number of CD34+ cells is usually ~5 × 10^6 when starting from 2 × 10^8 total cells (for 1 single isolation). The purified CD34+ cells were freshly injected. Human peripheral blood CD34+ cells were analyzed by flow cytometry. The following monoclonal anti-human antibodies were used to characterize the CD34 cell population: CD34-FITC (Becton, Dickinson and Company) and CD105-PE (Becton, Dickinson). Flow cytometric analysis demonstrated that CD34 cells did not express CD105 (0.2%) but did express CD34 (95%).

Activation of CD34+ cells to express TSG-6 in vitro
Human CD34+ cells and human fibroblasts (IMR-90) were plated at 50,000 cells/well in culture medium (α-minimum essential medium supplemented with 10% fetal bovine serum and 100 units/mL of...
Forty-mented with 10% fetal bovine serum. Total RNA was extracted (RNeasy Mini Kit; Qiagen) for reverse transcriptase polymerase chain reaction (RT-PCR) assays. Human fibroblasts (IMR-90) were obtained from the American Type Culture Collection (ATCC) and cultured in α-minimum essential medium supplemented with 10% fetal bovine serum.

Establishment of the ALI model of rats
Forty-five adult female, pathogen-free rats were given OA solution (10 μL/kg body weight, OA was suspended in PBS [Lonza Bioproducts]) intravenously via the tail vein. Ten minutes after OA injection, rats were randomly assigned to 3 groups: group C (ALLI, n = 15); group D (n = 15), which was intravenously injected with human fibroblasts IMR-90 (2 x 10^6 cells dissolved in 150 μL of PBS); and group E (n = 15), which was intravenously injected with CD 34+ve cells (2 x 10^6 cells dissolved in 150 μL of PBS). In addition, there were 2 control groups: control group A (n = 15), which did not receive any treatment, and control group B (n = 15), which was intravenously injected with PBS. Rats were sacrificed at 6, 24 and 48 h after OA administration. There were 5 rats in each group at each time point (6, 24 and 48 h after OA injection).

Blood and lung tissue sampling
Arterial blood samples (300 μL) were collected after scarification of the rats from the aortic artery via the opened chest into a heparinized syringe for measurement of arterial oxygen partial pressure (PaO₂) by blood gas analyzer (n = 5 per group) to assess hypoxia. Lungs were removed, and the right lung was weighed to examine the lung wet/dry weight ratio to detect edema. The left lung was divided into 2 parts: the first part was kept in formalin 10% to assess the lung injury and the response to CD 34+ve cell injection by histopathological examination with light microscope. The second part was stored in liquid nitrogen tank until total RNA and DNA extraction.

Lung wet/dry weight ratio
The wet weight of the immediate removed right lungs was recorded; lungs were then placed in an incubator at 60°C for 72 h, and the dry weight was detected. The wet lung mass divided by the dry lung mass represented the wet/dry lung ratio, which indicates the fraction of wet lung weight caused by water.

Light microscopic study
The specimens were fixed in 10% neutral-buffered formalin, dehydrated and embedded in paraffin; sections were then cut at 5 μm and stained with hematoxylin and eosin for routine histological examination [25].

PCR detection of human β actin gene
The presence of human β actin gene in the CD34+cells recipient rats was determined by PCR analysis according to Rajatileka et al. [26]. Amplification of the human β-actin gene; the housekeeping gene was performed by conventional PCR using forward primers: 5’-TGCCCATCTAGGAGGGGATG-3’ and reverse primer 5’-GAAATCGTGAGGTACCTAC-3’. Genomic DNA was extracted with phenol and chloroform from the rat lung. PCR was carried out in a final volume of 25 μL containing 2 μL (30 ng) of genomic DNA, 0.2 μmol/L of each primer and 10 μL of Taq PCR Master Mix (BIORON). The amplification protocol was as follows: 94°C for 10 min, then 35 cycles of 94°C for 1 min, 56°C for 45 s and 72°C for 45 s; then 72°C for 7 min, using heated lid thermal cycler. PCR products (325 bp) were separated with the use of 2% agarose gel electrophoresis.

Quantitative RT-PCR analysis for rat ICAM-1, TNF-α and IL-10
Total RNA was isolated from the lung tissue using an RNeasy Mini Kit including DNase I digestion following the manufacturer’s protocol (Qiagen, #74104). The RNA was then reverse transcribed using Quantiscript reverse transcriptase. Following reverse transcription, quantitative real-time PCR analysis was performed with a (Rotor-Gene Q 2plex, Qiagen) with SYBR green master mix (Roche Diagnostics). The primers were designed by the Primer 3 web-based tool (http://www-genome.wi.mit.edu/cgi-bin/primer/primer3_www.cgi) based on the published rat sequence. The following primers were used for analysis: rat ICAM-1, 5’-AAACCGGAGATGAATGGTACCTAC-3’ and 5’-TGCAGGTCCCTGGTGTACTC-3’; rat TNF-α, 5’-GGAAGAAATCTACGGCTGCTCCT-3’ and 5’-TCATACAGGGGCTTGAGCTCA-3’; rat IL-10, 5’-CCTTACTGCGGGCTTGAGC-3’; human TSG-6, 5’-GGCCATCGGTTCTCTCT-3’ and 5’-TCACACTGAAATCGAGTTAC-3’; human CD34, 5’-CAGCAGACATGAAATC-3’. The rat gene expression was normalized to rat cyclophilin B.
The human CD34+ progenitor cells were isolated from human peripheral blood mononuclear cells (PBMCs) with purity greater than 95%. The human peripheral blood mononuclear cells (PBMCs) plus human mononuclear cells were presented as mean ± SEM and significance was declared at \( P < 0.05 \).

**Results**

Human CD34+ progenitor cells were isolated from human peripheral blood mononuclear cells (PBMCs) with purity greater than 95%. The human \( \beta \) actin gene was detected in the lungs of the female rats that injected by CD34+ cells (group E) at 6 h after OA challenge; however, the lung of the rats in other groups (A, B, C and D) lacked this gene (Figure 1). This indicates that the injected human CD34+ cells had been successfully delivered into the lungs of the recipient rats.

**Effect of CD34+ cells transplantation on arterial oxygen partial pressure and lung water content**

There was no significant difference between control group A and control group B regarding arterial oxygen partial pressure (\( \text{PaO}_2 \); \( P > 0.05 \)). In groups C and D, OA-induced ALI significantly decreased \( \text{PaO}_2 \) (more severe hypoxemia) compared with the control groups A and B at 6 and 24 h after OA challenge (\( P < 0.05 \); Figure 2). Treatment with CD34+ cells resulted in a significant increase of \( \text{PaO}_2 \) (decreased hypoxia) in group E compared with group C at 6 and 24 h (\( P < 0.05 \)). There was no significant difference between all groups at 48 hours after OA challenge (\( P > 0.05 \); Figure 2).

There was no significant difference between control group A and control group B regarding wet/dry weight ratio (\( P > 0.05 \)). In groups (C and D), OA induced ALI increased lung wet/dry weight ratio (which is an indicator for lung edema) when compared with other groups at all time points (6, 24 and 48 h) after OA challenge (\( P < 0.05 \); Figure 2). Treatment with CD34+ cells significantly decreased pulmonary edema in group E at all time points compared with other groups (\( P < 0.05 \); Figure 2).

**Effect of CD34+ cells transplantation on lung histopathology**

Histopathological assessment of lung sections was done by hematoxylin and eosin staining to evaluate pulmonary architecture, tissue edema formation, infiltration of the inflammatory cells, congestion and hemorrhage (Figure 3). Lung sections of the control groups A and B showed no obvious lesion in the lung tissues (normal pulmonary architecture), that is, normal thickness of the interalveolar septum, normal bronchioles and blood vessels. In groups C and D, the lung sections displayed extensive morphological damage, manifested by the severe infiltration of numerous polymorphonuclear leukocytes and macrophages in the interstitial spaces, intra-alveolar and interstitial patchy congestion and hemorrhage, inter-alveolar septal thickening and interstitial edema. These pathological changes were greatest at 6 h and gradually reduced at 24 and 48 h. The administration of CD 34+ve cells in group E reduced the severity of lung injury and improved the lung histopathology compared with OA group C and OA+ human fibroblast group D at all time points. Assessment of lung sections of group E revealed markedly reduced hemorrhage, congestion, neutrophilic inflammation and interstitial edema, with preservation of alveoli in the

![Figure 1. Agarose gel electrophoresis of PCR product (325 bp) of human \( \beta \) actin gene: lane 1: positive results for rats received human CD34+ cells (group E) at 6 h after OA challenge; lane 2: positive results for rats received human CD34+ (group E) at 24 h after OA challenge; lane 3: positive results for rats received human CD34+ (group E) at 48 h after OA challenge; lane 4: negative result for rat received oleic acid (group G).](image)
lung tissue and the destruction of lung tissue was lighter compared with OA group C and OA + human fibroblast group D. These findings are suggesting that ALI induced by OA injection was attenuated by transplantation of CD34+ve cells.

**CD34+ cells are activated to express TSG-6 in vitro and in vivo**

There was significant increase of expression of TSG-6 from CD34+ cells incubated with TNF-α for 48 h than for 0, 6 and 24 h (P < 0.05). Interestingly, the response of CD34+ cells to TNF-α far exceeded the response of human fibroblasts (P < 0.05; Figure 4A). Real-time RT-PCR assays demonstrated that human TSG-6 mRNA in rat lung was increased at 6 h and further increased at 24 and 48 h after injection of CD34+ cells (Figure 4B). Surprisingly, TSG6 mRNA expression has not been investigated in lungs of rats received human fibroblasts.

**Effect of CD34+ cells transplantation on ICAM1, TNF-α and IL-10 gene expression**

Quantitative RT-PCR analysis revealed that there was a significant increase in the expression of pro-inflammatory factors such as ICAM-1 and TNF-α gene in the lungs of rats at 6, 24, and 48 h post-OA challenge (Figure 5). CD34+ cell treatment resulted in a drastic decrease of expression of these pro-inflammatory molecules. This result indicated that CD34+ transplantation mediates a reduction in pro-inflammatory activity in the OA-induced ALI rat.
We investigated levels of IL-10, a well-established anti-inflammatory factor, in the lung of OA-induced ALI rat collected in the presence or absence of CD34+ transplantation. Quantitative RT-PCR analysis revealed a significant increase in the expression of IL-10 in the lung of OA-induced ALI rat after CD34+ cells transplantation on various time points (6, 24 and 48 h) compared with other groups (Figure 5).
The promising cell-based therapeutic effect of human MSCs is limited because of a decrease in their regenerative potential with increasing donor age and the need for in vitro expansion before treatment [22]. In vitro cultivation may affect the character and effects of human adult stem cells because it can reduce MSC adhesion to laminin and endothelium [30] and cause MSCs to progressively lose their progenitor characteristics [31]. Thus, fresh isolation without in vitro expansion excludes the potential artificial effects from cultivation or other supplements in the medium. This prompted us to use freshly collected human peripheral blood CD34+ cells in this study.

One of the major early drawbacks to the therapeutic use of CD34+ cells was their relatively low basal density in the circulation. Fortunately, the discovery of agents that help to mobilize these cells from their resident bone marrow niche into the systemic circulation (where they can be collected and purified) considerably strengthened the field. The increase of circulating stem cells can be induced by administration of dextran sulfate or adenocorticortrophin and by strenuous physical exercise [23]. A similar technique, strenuous physical exercise, was adopted in this study to ensure progenitor cell mobilization to blood.

To our knowledge, this is the first study to indicate that freshly isolated human peripheral blood—derived CD34+ cells can be used as a novel and promising therapeutic and/or protective approach for OA-induced ALI. OA and LPS-exposed rodents displayed ALI presentation similar to that of human OA-induced ALI. OA and LPS-exposed rodents indicated by an increased lung wet/dry weight ratio, hypoxemia and increased capillary permeability), and alveolar infiltration of inflammatory cells [8,32–34]. Our results also showed a reduction in the wet/dry ratio and edema after CD34+ cells transplantation in OA-induced lung injury rats. Thus, treatment with CD34+ cells significantly decreased the pulmonary edema and improved the
lung wet/dry ratio. Likewise, pulmonary edema is relieved after administration of MSCs derived from bone marrow [4,9] or adipose tissue [35]. W also found that CD34+ cells transplantation reduces hypoxemia at 6 and 24 h after OA challenge. Chang et al. [36] also observed a remarkable increase in PaO₂ in a patient with ARDS after intratracheal administration of umbilical cord blood-derived MSCs. On the other hand, our results showed no significant difference of PaO₂ values between all groups at 48 h after OA challenge. These results were consistent with those of Xu et al. [4] and Kennedy et al. [5]. The improvement of PaO₂ at 48 h in the injured group may be due to hypoxic pulmonary vasoconstriction (HPV) through which the lung preserves oxygenation to the injured region [37,38]. Persistently increased lung microvascular permeability resulting in protein-rich lung edema is a hallmark of ALI/ARDS [39]. Thus, targeting microvascular leakiness to restore fluid homeostasis is a potential therapeutic approach for the prevention and treatment of ALI/ARDS. Histopathological analysis revealed that ALI rats (groups C and D) show intra-alveolar and interstitial patchy congestion and hemorrhage and interstitial edema. However, CD34+ treated rats (group E) show evidence of vascular improvement, reduction of hemorrhage and edema. Similar results have been observed by Huang et al. [22], who found that the freshly collected human umbilical cord derived CD34+ cells can restore vascular integrity in LPS-induced ALI mice. Another previous study has shown that these cells promote regeneration of injured alveolar epithelium in models of neonatal lung injury/bronchopulmonary dysplasia [40]. Other studies with human MSCs have shown decreased lung edema formation and lung vascular and epithelial barrier permeability in various animal models of ALI [8,41]. These data suggest that human CD34+ cells exhibit similar vascular protective effects as other adult stem cells. In contrast, Mao et al. [42] showed that in vitro expanded cord blood-derived CD34+ cells, but not freshly isolated CD34+ cells, induce lung growth and alveolarization in injured newborn lungs. This difference may be attributed to different animal models and different source of CD34+. This suggests that inhibition of inflammatory lung injury is mediated by mechanisms different from lung growth and alveolarization.

The mechanisms through which CD34+ cells exert their action is still unknown; however, it may be similar to other HSCs, such as MSCs, through paracrine and immunomodulatory mechanisms. Secretion of the paracrine-soluble factor Ang1 by human MSCs mainly restores epithelial protein permeability across primary cultures of human alveolar epithelial type II cell monolayer after cytomix-induced injury [43]. MSCs seem to induce macrophages to produce more IL-10 through the release of prostaglandin E2 [44]. MSCs could down-regulate the inflammatory process by decreasing the pro-inflammatory cytokine expression such as TNF-α and secreting anti-inflammatory agents such as IL-10, IL-1Ra, IL-13, angiopoietin-1 and keratinocyte growth factor [43,45]. Recently, Huang et al. [22] demonstrated that freshly isolated human cord blood-derived CD34+ cells were protective against inflammatory lung injury induced by LPS challenge. They also observed drastic decrease of expression of proinflammatory molecules including TNF-α, IL-6, ICAM-1 and iNOS in CD34+ treated lungs [22]. Consistent with this, our data showed that the

Figure 5. Graphical presentation of real-time quantitative PCR analysis of the expression of pro-inflammatory genes such as TNF-α and ICAM1, as well as anti-inflammatory gene IL-10, in OA-induced ALI rats with or without CD34+ cell therapy at various time points (6, 24 and 48 h). The housekeeping gene encoding cyclophilin B was used as an internal reference for normalization. Data expressed as mean ± SEM (n = 3 in triplicate). The expression level of each target gene in control rat (group A) at various time points was considered the baseline. *Means carrying different superscripts at the same time point are significantly differed at P ≤ 0.05 based on least significant difference.
improvement in lung injury was associated with a decrease of expression of proinflammatory molecules including TNF-α and ICAM-1, as well as an increase of the expression of anti-inflammatory molecule IL-10.

The anti-inflammatory effects of CD34+ cells in ALI model may be attributed to their activation to secrete TSG-6. We found significant increase of the expression of TSG-6 after activation of CD34+ cells in vitro. Also, human TSG-6 gene was significantly upregulated in rats treated with CD34+ cells in vivo. The upregulation of the TSG-6 was of special interest because of the known anti-inflammatory effects of the protein [46,47]. TSG-6 is a 35-kDa secreted protein produced by many cell types in response to TNF-α and IL-1β [46,47]. In transgenic mice, inactivation of the TSG-6 gene increased inflammatory responses [48], and overexpression of the gene decreased inflammatory responses [49].

Danchuk et al. [8] found that hMSCs in the LPS-exposed lung upregulated their TSG-6 mRNA expression more than 900-fold and suggested that the anti-inflammatory properties of hMSCs in the lung are explained by activation of hMSCs to secrete TSG-6. Lee et al. [50] indicated that the hMSCs that were trapped in the lung were activated to secrete TSG-6, and the TSG-6 suppressed the excessive inflammatory response in murine myocardial infarction model. We first studied the activation of CD34+ cells to express TSG-6; however, our results did not exclude the possibility that the CD34+ cells secreted other anti-inflammatory factors in addition to TSG-6. A previous study by Majka et al. [51] reported that human CD34+ cells release numerous growth factors and cytokines. Krenning et al. [52] reported that CD34+ cells modulate proliferation and endothelial differentiation of CD14+ cells by releasing hepatocyte growth factor, IL-8 and monocyte chemoattractant protein 1 (MCP-1). Recently, CD34+ cells were shown to secrete interleukins, growth factors and chemokines that are capable of accelerating vascular network formation in vivo and enhancing healing of ischemic ulcers in diabetic mice [53]. Culture-derived progenitor cells release IL-8, producing a mitogenic effect on vascular endothelial cells [54].

Conclusions

Our study has demonstrated that intravenous administration of CD34+ cells freshly isolated from human peripheral blood attenuates OA-induced lung injury in rat model primarily by down-modulating the inflammatory process. TSG-6 protein secreted from CD34+ cells could involve in modulating the inflammation. Given the easy availability without defects from in vitro culture, CD34+ cells may be an important source of stem cells for the treatment of ALI/ARDS. However, further investigations are needed to determine the optimal dose and safety of CD34+ cells and their ability to prevent ALI/ARDS in high-risk groups so that improved clinical outcomes can be ascertained.

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