Tatiana Maron-Gutierrez[1], Indianara Araujo[2], Marcelo Marcos Morales[3], Cristiane Sousa Nascimento Baez Garcia[4], Patricia Rieken Macedo Rocco[5]

Stem cell therapy in acute respiratory distress syndrome

Terapia com células-tronco na síndrome do desconforto respiratório agudo

1. Post-graduate student (Master) in Physiology from the Instituto de Biofísica Carlos Chagas Filho da Universidade Federal do Rio de Janeiro – UFRJ – Rio de Janeiro (RJ), Brazil.
2. Post-graduate student (Doctorate) in Physiology from the Instituto de Biofísica Carlos Chagas Filho da Universidade Federal do Rio de Janeiro – UFRJ – Rio de Janeiro (RJ), Brazil
3. PhD, Associate Professor of the Universidade Federal do Rio de Janeiro – UFRJ – Rio de Janeiro (RJ), Brazil.
4. Researcher from the Laboratório de Investigação Pulmonar, Instituto de Biofísica Carlos Chagas Filho da Universidade Federal do Rio de Janeiro – UFRJ – Rio de Janeiro (RJ), Brazil.
5. PhD, Associate Professor of the Universidade Federal do Rio de Janeiro – UFRJ – Rio de Janeiro (RJ), Brazil.

Received from the Pulmonary Research Laboratory from the Instituto de Biofísica Carlos Chagas Filho da Universidade Federal do Rio de Janeiro - UFRJ – Rio de Janeiro (RJ), Brazil.

Financial support: Centers of Excellence Program – Science and Technology Ministry (PRONEX-FAPERJ), National Council for Scientific and Technological Development (CNPq), Carlos Chagas Filho Foundation for Research Support of the State of Rio de Janeiro (FAPERJ),Millennium Institute (INOFAR).

Submitted on July 28, 2008
Accepted on February 4, 2009

Author for correspondence:
Patricia Rieken Macedo Rocco
Laboratório de Investigação Pulmonar - Instituto de Biofísica Carlos Chagas Filho Universidade Federal do Rio de Janeiro
Avenida Carlos Chagas Filho, s/n, Bloco G-014, Cidade Universitária, Ilha do Fundão
CEP: 21941-902 - Rio de Janeiro (RJ), Brazil.
Phone: +55 (21) 2562-6530/
Fax: +55 (21) 2280-8193
E-mail: prmrocco@biof.ufrj.br

ABSTRACT

Acute respiratory distress syndrome is characterized by an acute pulmonary inflammatory process induced by the presence of a direct (pulmonary) insult that affects lung parenchyma, or an indirect (extrapulmonary) insult that results from an acute systemic inflammatory response. It is believed that an efficient therapy for the acute respiratory distress syndrome should attenuate inflammatory response and promote adequate repair of the lung injury. This article presents a brief review on the use of stem cells and their potential therapeutic effect on the acute respiratory distress syndrome. This systematic review was based upon clinical and experimental acute respiratory distress syndrome studies included in the MedLine and SciElO database during the last 10 years. Stem cell transplant lead to an improvement in lung injury and fibrotic process by inducing adequate tissue repair. This includes alveolar epithelial cell differentiation,and also reduces pulmonary and systemic inflammatory mediators and secretion of growth factors. Stem cells could be a potential therapy for acute respiratory distress syndrome promoting lung repair and attenuating the inflammatory response. However, mechanisms involving their anti-inflammatory and antifibrinogenic effects require better elucidation, limiting their immediate clinical use in acute respiratory distress syndrome.

Keywords: Respiratory distress syndrome, adult/therapy; Stem cells; Pulmonary fibrosis

INTRODUCTION

The acute respiratory distress syndrome (ARDS) is characterized by a diffuse inflammatory reaction of the pulmonary parenchyma, with increase of alveolar-capillary permeability associated to a series of clinical, radiological and physiological anomalies.[1,2] ARDS may be induced by a direct insult to the alveolar epithelium (pulmonary ARDS) or indirect insult through the vascular endothelium (extrapulmonary ARDS) where the lung injuries are caused by circulating inflammatory mediators that results from an acute systemic inflammatory response (i.e. peritonitis) (Figure 1).

After a direct insult, epithelial damage leads to alveolar edema, reduction in the removal of edema fluid from the alveolar space, decreased production and turnover of the surfactant and pulmonary fibrosis. Efficient alveolar epithelial repair may reduce the development of fibrosis, since the

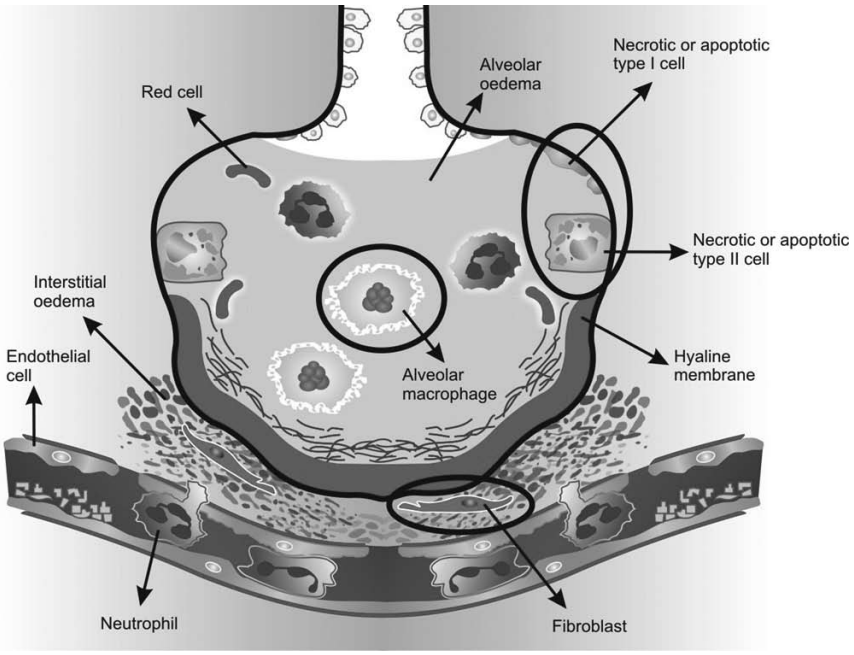

Figure 1 – Schematic representation of the Acute Respiratory Distress Syndrome (ARDS) pathophysiology. ARDS may be induced by a direct insult to the alveolar epithelium (pulmonary ARDS) or indirect through the vascular endothelium (extrapulmonary ARDS). ARDS is characterized by a diffuse inflammatory reaction of the pulmonary parenchyma, leading to alveolar and interstitial edema, infiltration of inflammatory cells (i.e. neutrophils), formation of hyaline membrane, reduction of the alveolar fluid clearance, decreased production and turnover of surfactant (injury of type II pneumocytes) and lung fibrosis. Cell therapy may act repairing the alveolar epithelium and alveolar capillary injury, reducing the release of inflammatory mediators and of fibrogenesis.

presence of an intact alveolar epithelial layer suppresses fibroblast proliferation and matrix deposition.[3] Epithelial repair involves several complex molecular mechanisms, including interactions between the alveolar type II cell, mesenchymal cells, endothelial cells and the matrix.[3]

In extrapulmonary ARDS, damage to the microvascular endothelium, initially induces interstitial edema and neutrophilic infiltration.[3] The pulmonary endothelium is a highly specialized tissue, that possesses several physiological, immunological and synthetic functions, in addition, the endothelium also holds several enzymes, receptors and transduction molecules, which interact with one another and with the components of the capillary wall and circulating blood cells.[4] The alveolar-capillary barrier mediates changes in permeability and is critical for the repair and remodeling of the alveolar capillary membrane.[4]

Due to the severity of ARDS, advanced methods for life support such as the use of mechanical ventilation and potent drug therapies are adopted.[5,6] However, despite advances in the management of ARDS, mortality remains high, approximately 40%.[7-9]

It is believed that an effective therapy for treatment of ARDS should promote both attenuation of inflammatory response and appropriate repair of lung tissue.[10] In this context, stem cells could present a therapeutic potential for ARDS due to modulation of the inflammatory process and remodeling in pulmonary diseases.[11]

PROPERTIES OF STEM CELLS

Stem cells are undifferentiated cells with the ability of self-renewal (generate copies identical of themselves) and to differentiate into various cells of the organism. Regarding the cell differentiation potential, stem cells may be classified as 1) totipotent; 2) pluripotent; 3) multipotent and 4) unipotent cells (Chart 1).[12,13]

Totipotent and pluripotent cells have the ability to form all lineages of body. They present high proliferation capacity and are essentially found in the embryo. Totipotent cells are found in the first stages of the embryo (3 to 4 days of life), when the embryo has 16 to 32 cells, while pluripotent cells can be found after this stage. Another difference between totipotent and pluripotent cells is the capacity of totipotent cells to also originate the placenta and embryonic annexes.

Four to five days after fecundation, the blastocyte is

Chart 1 – Classification related to cell differentiation potential

Term	Definition	Example
Totipotent	Ability to form the embryo and fertilized trophoblast of the placenta	Oocyte or zygote
Pluripotent	Ability to differentiate into almost all cells of the three germ layers	Embryonic stem cells
Multipotent	Ability to originate cell types of their original tissue site	Mesenchymal stem cells Hematopoietic stem cells
Unipotent	Ability to generate one single cell type	Type II pneumocyte, that may generate type I pneumocyte

formed, which is comprised by trophoblasts and by the cells of the inner mass. Embryonic stem cells are cells isolated from the inner mass of early developing blastocysts and have the capacity for self-renewal and are pluripotent cells,[14] having the ability to differentiate into cells of all embryologic lineages and all adult cell types from the three germ layers: endoderm, mesoderm and ectoderm.[15] In this context Rippon et al.[16] showed that embryonic stem cells in a specific culture medium may originate lung progenitor cells and have several advantages: (1) better cell integration with the host tissue, (2) division capacity after implantation, minimizing the number of cells that must be transplanted and (3) capacity to generate one or more types of adult somatic cells, such as pneumocytes type I, II and Clara cells.[16] Notwithstanding their extensive therapeutic potential, safety measures related to the possibility of the embryonic stem cells forming *in vivo* tumors and occurrence of chromosomal instability, restrict their use.[17] Furthermore, due to ethical issues, the use of embryonic stem cells is considered to be controversial.

Adult stem cells are isolated from adult tissues including bone marrow, adipose tissue, nervous tissue, umbilical cord blood, and placenta that have the capacity for self-renewal.[18] In general, adult stem cells are multipotent, having the capacity to differentiate into mature cell types of the parent tissue. Some populations of adult stem cells, such as bone marrow-derived mesenchymal stem cells, exhibit a range of lineage differentiation that is not limited to a single tissue type and is not restricted to the parent tissue.[14] Unipotent stem cells may only generate one cell type, but still have self-renewal capacity.

The bone marrow is the source of two distinct populations of stem cells, the hematopoietic stem cells (HSC), that have the capacity for self-renewal and ability to differentiate into the blood cell lineages including leukocytes, erythrocytes and platelets[19], and the mesenchymal stem cells (MSC), which are cells of stromal origin that can self-renew and have the ability to differentiate into a variety of cell lineages, such as,osteoblasts, chondrocytes, adipocytes[20,21], skeletal muscles[22] , cardiac muscle, endothelial cells, hepatocytes, neurons, oligodentrocytes and astrocytes.[20,21,23]

The mechanisms by which stem cells assume pulmonary phenotypes remain unclear.[24] It is believed that transdifferentiation, defined as the capacity of a differentiated somatic cell to acquire the phenotype of a differentiated cell of the same or different lineage, may be one of the mechanisms. However, in the past few years, transdifferentiation has been questioned,[25] while other phenomena have been considered responsible for the greater proliferation capacity of the adult stem cells, such as for instance, cell fusion. Cell fusion of adult bone marrow-derived stem cells with pulmonary epithelial cells may take place under various circumstances *in vitro,* but this phenomenon apparently does not occur as often *in vivo*.[26,27] It is believed that adult stem cells are recruited to the site of the injury after the release of chemotactic signals and/or increased expression of specific adhesion molecules.[20,25,27-30] Another factor that remains unclear is the mechanism by which adult stem cells manage to cross the basal membrane of the lung and reach the injured areas. Considering that such phenomenon follows the same mechanism by which defense cells reach their target, it is believed that the membrane permeability is regulated by production of proteins synthesized by the tissue itself, controlling the influx of stem cells to the injured area.[14,31,32]

STEM CELL THERAPY IN THE ACUTE RESPIRATORY DISTRESS SYNDROME

Therapy with bone marrow-derived stem cells not only acts modulating the inflammatory process but also promotes alveolar epithelium repair, minimizing fibrosis,[33-35] as the presence of an intact epithelial layer sup-

presses proliferation of fibroblasts and extracellular matrix deposition.[25]

Yamada et al.[35] showed that the inflammatory stimulus promotes the recruitment of progenitor cells from bone marrow into the systemic circulation, with further differentiation in epithelial and endothelial cells repairing the lung injury. Since the inflammatory stimulus induces recruitment of bone marrow-derived progenitor cells to the injured site, the use of gene therapy associated to the progenitor cells, could facilitate pulmonary repair. Therefore, the use of progenitor cells may represent a new therapeutic intervention for the ARDS.

Other studies suggest that intravenous or intrapulmonary administration of mesenchymal stem cells can prevent the inflammatory process in experimental models of acute pulmonary injury.[31,36-40] Mesenchymal stem cells were initially isolated by Friedenstein et al.[39] based upon their plastic adherence when maintained in standard culture conditions using culture flasks , and their great differentiation potential. It was observed that mesenchymal stem cells reduce the levels of pro-inflammatory cytokines, increasing the release of anti-inflammatory cytokines and soluble factors that ultimately induce phenotype conversion. Mesenchymal stem cells may also act inhibiting the activation of dendritic cells and T lymphocytes.[31,34,37] In an experimental model of acute lung injury (ALI), Gupta et al. showed that intratracheal instillation of mesenchymal stem cells reduced the inflammatory process by decreasing inflammatory mediators [macrophage inflammatory protein (MIP)-2 and tumor necrosis factor (TNF)- α], independently from the differentiation mechanism.[36] At the same time, Xu et al. were not able to detect the presence of mesenchymal stem cells in the pulmonary parenchyma in an experimental model of ALI, although cell therapy had reduced the systemic inflammatory response, suppressing the production of pro-inflammatory cytokines and stimulating the release of anti-inflammatory cytokines.[37] On the other hand, Mei et al. observed that, when administered alone, MSCs minimized pulmonary inflammation in a model of ALI induced by lipopolysaccharide (LPS);[34] however, the administration of MSCs transfected with angiopoietin-1 resulted in an improvement of the inflammatory process, reducing the levels of various cytokines and chemokines in the bronchoalveolar lavage fluid, leading to a reduction of permeability and consequent leakage of plasma. Moreover, the increased production of angiopoietin-1 by MSCs genetically modified, reduced the production of molecules of adhesion, minimizing the influx of inflammatory cells into the alveolar space.[34] In this context, mesenchymal stem cells seem to partially act through paracrine mechanisms, since the animals treated with mesenchymal stem cells had a reduced production of pro-inflammatory cytokines and an increase of the levels of anti-inflammatory cytokines.[41] However, the potential of stem cells in remodeling the alveolar epithelium remains controversial.[42]

Endothelial progenitor cells (EPC) have also shown a high proliferative potential and can migrate to regions of the circulatory system where there is vascular injury, including traumatic, degenerative, inflammatory or ischemic injuries, promoting repair or angiogenesis.[10,43-45] In an experimental model of acute lung injury it was shown that EPCs, when intravenously administered, incorporate into the pulmonary endothelium. EPCs may play a relevant role in reestablishing the integrity of the pulmonary endothelium and contributing to the repair process.[44] A recent study by Lam et al.[46] demonstrated that the administration of EPCs attenuated lung injury and pulmonary endothelium dysfunction. The authors observed the decrease of the dry/wet weight (index of pulmonary edema), formation of hyaline membrane, hemorrhage and neutrophil infiltration into alveolar space, suggesting an important role of EPCs in repairing the endothelium and in the preservation of pulmonary alveolar-capillary barrier. These effects appear to be mediated by EPCs anti-oxidative enzymes high activity and its cytoprotector effect.

Clinical studies also suggest that the high presence of circulating levels of endothelial progenitor cells are directly related to the survival of ARDS patients.[43,47] Yamada et al.[48] showed, in patients with pneumonia, that persistent fibrotic changes were observed in those with low circulating levels of EPCs, suggesting an important role of these cells in the repair of lung tissue. In this context, the increase of the number of bone marrow derived progenitor cells may contribute to alveolar repair and a decrease in mortality in patients with ALI/ARDS.[10]

CONCLUSION

In spite of the few clinical studies, stem cells may in the future play an important role in acute lung injury/acute respiratory distress syndrome, modulating the inflammatory process, inhibiting fibrogenesis and promoting tissue repair, thereby reducing its mortality. However, additional studies are required for a better understanding of the effects of stem cells on ALI/ARDS.

RESUMO

A síndrome do desconforto respiratório agudo é caracterizada por uma reação inflamatória difusa do parênquima pulmonar, podendo ser induzida por um insulto direto ao epitélio alveolar (síndrome do desconforto respiratório agudo pulmonar) ou indireto através do endotélio vascular (síndrome do desconforto respiratório agudo extrapulmonar). Acredita-se que uma terapia eficaz para o tratamento da síndrome do desconforto respiratório agudo deva atenuar a resposta inflamatória e promover adequado reparo da lesão pulmonar. O presente artigo apresenta uma breve revisão acerca do potencial terapêutico das células-tronco na síndrome do desconforto respiratório agudo. Essa revisão bibliográfica baseou-se em uma pesquisa sistemática de artigos experimentais e clínicos sobre terapia celular na síndrome do desconforto respiratório agudo incluídos nas bases de dados MedLine e Scielo nos últimos 10 anos. O transplante de células-tronco promove melhora da lesão inflamatória pulmonar e do conseqüente processo fibrótico, induzindo adequado reparo tecidual. Dentre os mecanismos envolvidos, podemos citar: diferenciação em células do epitélio alveolar e redução na liberação de mediadores inflamatórios e sistêmicos e fatores de crescimento. A terapia com células-tronco derivadas da medula óssea pode vir a ser uma opção eficaz e segura no tratamento da síndrome do desconforto respiratório agudo por acelerar o processo de reparo e atenuar a resposta inflamatória. Entretanto, os mecanismos relacionados à atividade antiinflamatória e antifibrogênica de tais células necessitam ser mais bem elucidados, limitando, assim, o seu uso clínico imediato.

Descritores: Síndrome do desconforto respiratório do adulto/terapia; Células-tronco; Fibrose pulmonar

REFERENCES

1. Bernard GR. Acute respiratory distress syndrome: a historical perspective. Am J Respir Crit Care Med. 2005;172(7):798-806.
2. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med. 1994;149(3 Pt 1):818-24. Review.
3. Rocco PR, Pelosi P. Pulmonary and extrapulmonary acute respiratory distress syndrome: myth or reality? Curr Opin Crit Care. 2008;14(1):50-5.
4. Orfanos SE, Mavrommati I, Korovesi I, Roussos C. Pulmonary endothelium in acute lung injury: from basic science to the critically ill. Intensive Care Med. 2004;30(9):1702-14.
5. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med. 1998;338(6):347-54. Comment in: N Engl J Med. 1998;339(3):196-7; author reply 198-9. N Engl J Med. 1998;339(3):197; author reply 198-9.
6. Cepkova M, Matthay MA. Pharmacotherapy of acute lung injury and the acute respiratory distress syndrome. J Intensive Care Med. 2006;21(3):119-43. Review.
7. Artigas A, Bernard GR, Carlet J, Dreyfuss D, Gattinoni L, Hudson L, et al. The American-European Consensus Conference on ARDS, part 2: Ventilatory, pharmacologic, supportive therapy, study design strategies, and issues related to recovery and remodeling. Acute respiratory distress syndrome. Am J Respir Crit Care Med. 1998;157(4 Pt 1):1332-47.
8. Brun-Buisson C, Minelli C, Bertolini G, Brazzi L, Pimentel J, Lewandowski K, Bion J, Romand JA, Villar J, Thorsteinsson A, Damas P, Armaganidis A, Lemaire F; ALIVE Study Group. Epidemiology and outcome of acute lung injury in European intensive care units. Results from the ALIVE study. Intensive Care Med. 2004;30(1):51-61. Comment in: Intensive Care Med. 2004;30(1):4-6.
9. Villar J, Pérez-Méndez L, López J, Belda J, Blanco J, Saralegui I, Suárez-Sipmann F, López J, Lubillo S, Kacmarek RM; HELP Network. An early PEEP/FIO2 trial identifies different degrees of lung injury in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 2007;176(8):795-804. Comment in: Am J Respir Crit Care Med. 2008;177(6):670; author reply 671.
10. Kubo H. Is cell therapy in acute lung injury a realistic dream? Am J Respir Crit Care Med. 2005;172(7):794-5. Comment on: Am J Respir Crit Care Med. 2005;172(7):854-60.
11. Kotton DN, Summer R, Fine A. Lung stem cells: new paradigms. Exp Hematol. 2004;32(4):340-3.
12. van Haaften T, Thébaud B. Adult bone marrow-derived stem cells for the lung: implications for pediatric lung diseases. Pediatr Res. 2006;59(4 Pt 2):94R-9R.
13. Majka M, Kucia M, Ratajczak MZ. Stem cell biology - a never ending quest for understanding. Acta Biochim Pol. 2005;52(2):353-8.
14. Weiss DJ, Kolls JK, Ortiz LA, Panoskaltsis-Mortari A, Prockop DJ. Stem cells and cell therapies in lung biology and lung diseases. Proc Am Thorac Soc. 2008;5(5):637-67.
15. Griffiths MJ, Bonnet D, Janes SM. Stem cells of the alveolar epithelium. Lancet. 2005;366(9481):249-60.
16. Rippon HJ, Polak JM, Qin M, Bishop AE. Derivation of distal lung epithelial progenitors from murine embryonic stem cells using a novel three-step differentiation protocol.

Stem Cells. 2006;24(5):1389-98.

17. Carpenter MK, Rosler ES, Fisk GJ, Brandenberger R, Ares X, Miura T, et al. Properties of four human embryonic stem cell lines maintained in a feeder-free culture system. Dev Dyn. 2004;229(2):243-58.
18. Aliotta JM, Passero M, Meharg J, Klinger J, Dooner MS, Pimentel J, Quesenberry PJ. Stem cells and pulmonary metamorphosis: new concepts in repair and regeneration. J Cell Physiol. 2005;204(3):725-41.
19. Grove JE, Bruscia E, Krause DS. Plasticity of bone marrow-derived stem cells. Stem Cells. 2004;22(4):487-500. Review.
20. Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, et al. Multilineage potential of adult human mesenchymal stem cells. Science. 1999;284(5411):143-7.
21. Prockop DJ. Marrow stromal cells as stem cells for nonhematopoietic tissues. Science. 1997;276(5309):71-4. Review.
22. Ferrari G, Cusella-De Angelis G, Coletta M, Paolucci E, Stornaiuolo A, Cossu G, Mavilio F. Muscle regeneration by bone marrow-derived myogenic progenitors. Science. 1998;279(5356):1528-30. Erratum in: Science. 1998;281(5379):923. Comment in: Science. 1998;279(5356):1456.
23. Jiang Y, Jahagirdar BN, Reinhardt RL, Schwartz RE, Keene CD, Ortiz-Gonzalez XR, et al. Pluripotency of mesenchymal stem cells derived from adult marrow. Nature. 2002;418(6893):41-9. Erratum in: Nature. 2007;447(7146):879-80. Comment in: Nature. 2002;418(6893):1. Nature. 2002;418(6893):25-7. Nature. 2007;447(7146):763.
24. Prockop DJ. "Stemness" does not explain the repair of many tissues by mesenchymal stem/multipotent stromal cells (MSCs). Clin Pharmacol Ther. 2007;82(3):241-3.
25. Krause DS. Bone marrow-derived cells and stem cells in lung repair. Proc Am Thorac Soc. 2008;5(3):323-7.
26. Neuringer IP, Randell SH. Stem cells and repair of lung injuries. Respir Res. 2004;5:6.
27. Weiss DJ, Berberich MA, Borok Z, Gail DB, Kolls JK, Penland C, Prockop DJ. Adult stem cells, lung biology, and lung disease. NHLBI/Cystic Fibrosis Foundation Workshop. Proc Am Thorac Soc. 2006;3(3):193-207.
28. Loi R, Beckett T, Goncz KK, Suratt BT, Weiss DJ. Limited restoration of cystic fibrosis lung epithelium in vivo with adult bone marrow-derived cells. Am J Respir Crit Care Med. 2006;173(2):171-9.
29. Weiss DJ. Stem cells and cell therapies for cystic fibrosis and other lung diseases. Pulm Pharmacol Ther. 2008;21(4):588-94.
30. Takahashi M, Li TS, Suzuki R, Kobayashi T, Ito H, Ikeda Y, et al. Cytokines produced by bone marrow cells can contribute to functional improvement of the infarcted heart by protecting cardiomyocytes from ischemic injury. Am J Physiol Heart Circ Physiol. 2006;291(2):H886-93.
31. Rojas M, Xu J, Woods CR, Mora AL, Spears W, Roman J, Brigham KL. Bone marrow-derived mesenchymal stem cells in repair of the injured lung. Am J Respir Cell Mol Biol. 2005;33(2):145-52.
32. Kotton DN, Ma BY, Cardoso WV, Sanderson EA, Summer RS, Williams MC, Fine A. Bone marrow-derived cells as progenitors of lung alveolar epithelium. Development. 2001;128(24):5181-8.
33. Aliotta JM, Keaney P, Passero M, Dooner MS, Pimentel J, Greer D, et al. Bone marrow production of lung cells: the impact of G-CSF, cardiotoxin, graded doses of irradiation, and subpopulation phenotype. Exp Hematol. 2006;34(2):230-41.
34. Mei SH, McCarter SD, Deng Y, Parker CH, Liles WC, Stewart DJ. Prevention of LPS-induced acute lung injury in mice by mesenchymal stem cells overexpressing angiopoietin 1. PLoS Med. 2007;4(9):e269.
35. Yamada M, Kubo H, Kobayashi S, Ishizawa K, Numasaki M, Ueda S, et al. Bone marrow-derived progenitor cells are important for lung repair after lipopolysaccharide-induced lung injury. J Immunol. 2004;172(2):1266-72. Erratum in: J Immunol. 2004;173(7):4755.
36. Gupta N, Su X, Popov B, Lee JW, Serikov V, Matthay MA. Intrapulmonary delivery of bone marrow-derived mesenchymal stem cells improves survival and attenuates endotoxin-induced acute lung injury in mice. J Immunol. 2007;179(3):1855-63.
37. Xu J, Woods CR, Mora AL, Joodi R, Brigham KL, Iyer S, Rojas M. Prevention of endotoxin-induced systemic response by bone marrow-derived mesenchymal stem cells in mice. Am J Physiol Lung Cell Mol Physiol. 2007;293(1):L131-41.
38. Wong AP, Dutly AE, Sacher A, Lee H, Hwang DM, Liu M, et al. Targeted cell replacement with bone marrow cells for airway epithelial regeneration. Am J Physiol Lung Cell Mol Physiol. 2007;293(3):L740-52.
39. Friedenstein AJ, Chailakhyan RK, Latsinik NV, Panasyuk AF, Keiliss-Borok IV. Stromal cells responsible for transferring the microenvironment of the hemopoietic tissues. Cloning in vitro and retransplantation in vivo. Transplantation. 1974;17(4):331-40.
40. Ortiz LA, Dutreil M, Fattman C, Pandey AC, Torres G, Go K, Phinney DG. Interleukin 1 receptor antagonist mediates the antiinflammatory and antifibrotic effect of mesenchymal stem cells during lung injury. Proc Natl Acad Sci U S A. 2007;104(26):11002-7.

41. Matthay MA. Treatment of acute lung injury: clinical and experimental studies. Proc Am Thorac Soc. 2008;5(3):297-9.
42. Kotton DN, Fabian AJ, Mulligan RC. Failure of bone marrow to reconstitute lung epithelium. Am J Respir Cell Mol Biol. 2005;33(4):328-34.
43. Burnham E, Moss M. Progenitor cells in acute lung injury. Minerva Anestesiol. 2006;72(6):369-74.
44. Kähler CM, Wechselberger J, Hilbe W, Gschwendtner A, Colleselli D, Niederegger H, et al. Peripheral infusion of rat bone marrow derived endothelial progenitor cells leads to homing in acute lung injury. Respir Res. 2007;8:50.
45. Young PP, Vaughan DE, Hatzopoulos AK. Biologic properties of endothelial progenitor cells and their potential for cell therapy. Prog Cardiovasc Dis. 2007;49(6):421-9.
46. Lam CF, Liu YC, Hsu JK, Yeh PA, Su TY, Huang CC, et al. Autologous transplantation of endothelial progenitor cells attenuates acute lung injury in rabbits. Anesthesiology. 2008;108(3):392-401. Comment in: Anesthesiology. 2008;108(3):354-6.
47. Burnham EL, Taylor WR, Quyyumi AA, Rojas M, Brigham KL, Moss M. Increased circulating endothelial progenitor cells are associated with survival in acute lung injury. Am J Respir Crit Care Med. 2005;172(7):854-60. Comment in: Am J Respir Crit Care Med. 2005;172(7):794-5.
48. Yamada M, Kubo H, Ishizawa K, et al. Increased circulating endothelial progenitor cells in patients with bacterial pneumonia: evidence that bone marrow derived cells contribute to lung repair. Thorax. 2005;60(5):410-3.