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REVIEW

Stem/progenitor cells and obstructive sleep apnea syndrome - new insights for clinical applications

Miruna Mihaela Micheu, Ana-Maria Rosca, Oana-Claudia Deleanu

Miruna Mihaela Micheu, Department of Cardiology, Clinical Emergency Hospital of Bucharest, 014461 Bucharest, Romania

Ana-Maria Rosca, Department of Regenerative Medicine, "Nicolae Simionescu" Institute for Cellular Biology and Pathology, 050568 Bucharest, Romania

Oana-Claudia Deleanu, "Carol Davila" University of Medicine and Pharmacy, 050474 Bucharest, Romania

Oana-Claudia Deleanu, "Marius Nasta" Institute of Pneumophtisiology Bucharest, 050159 Bucharest, Romania

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Correspondence to: Miruna Mihaela Micheu, MD, PhD, Department of Cardiology, Clinical Emergency Hospital of Bucharest, Floreasca street 8, 014461 Bucharest, Romania. mirunamicheu@yahoo.com
Telephone: +4-07-22451755

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Abstract

Obstructive sleep apnea syndrome (OSAS) is a widespread disorder, characterized by recurrent upper airway obstruction during sleep, mostly as a result of complete or partial pharyngeal obstruction. Due to the occurrence of frequent and regular hypoxic events, patients with OSAS are at increased risk of cardiovascular disease, stroke, metabolic disorders, occupational errors, motor vehicle accidents and even death. Thus, OSAS has severe consequences and represents a significant economic burden. However, some of the consequences, as well as their costs can be reduced with appropriate detection and treatment. In this context, the recent advances that were made in stem cell biology knowledge and stem cell - based technologies hold a great promise for various medical conditions, including respiratory diseases. However, the investigation of the role of stem cells in OSAS is still recent and rather limited, requiring further studies, both in animal models and humans. The goal of this review is to summarize the current state of knowledge regarding both lung resident as well as circulating stem/progenitor cells and discuss existing controversies in the field in order to identify future research directions for clinical applications in OSAS. Also, the paper highlights the requisite for inter-institutional, multi-disciplinary research collaborations in order to achieve breakthrough results in the field.

Key words: Obstructive sleep apnea syndrome; Continuous positive airway pressure therapy; Lung resident stem/progenitor cells; Circulating stem/progenitor cells; Lung homeostasis

Core tip: Obstructive sleep apnea syndrome (OSAS) is a widespread disorder characterized by recurrent upper airway obstruction during sleep, resulting in severe consequences such as increased risk of cardiovascular disease, stroke, metabolic disorders, occupational errors,

motor vehicle accidents and even death. However, the consequences and their costs can be reduced with appropriate detection and treatment. The goal of this review is to summarize the current state of knowledge regarding both lung resident as well as circulating stem/progenitor cells and to discuss existing controversies in the field in order to identify future research directions for clinical applications in OSAS.

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INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a prevalent condition with serious undesirable consequences and significant economic burden[1-4]. It is characterized by recurrent upper airway obstruction during sleep, due mostly to complete or partial pharyngeal obstruction. As a result, sleep fragmentation and repetitive hypoxemia occur, leading to excessive daytime sleepiness, activation of sympathetic nervous system, endothelial dysfunction and hemodynamic changes. Consequently, patients with OSAS are at increased risk of cardiovascular disease, stroke, metabolic disorders, occupational errors, motor vehicle accidents and even death. Health and public consequences, as well as their costs can be reduced with appropriate identification and treatment[2,5].

The current treatment includes the use of continuous positive airway pressure (CPAP) or oral devices which must be worn at night to help normal breathing. However, the use of such devises raises the problem of patients' adherence to therapy.

Recent development of scientific methods and understandings of stem cell biology have led to an explosion of interest in stem-cell research; consequently, stem cell - based technologies and therapies soon became one of the most rapidly expanding areas, holding a great promise for various medical conditions.

The goal of this review is to summarize the current state of knowledge regarding both lung resident as well as circulating stem/progenitor cells and discuss existing controversies in the field in order to identify future research directions for clinical applications in OSAS.

LUNG RESIDENT STEM/PROGENITOR CELLS

Several varieties of human lung resident stem/progenitor cells have been isolated and identified both *in vivo* and *in vitro*. Broadly, they comprise three major cell types, which are summarized in Table 1: Epithelial stem/progenitor cells, endothelial progenitor cells (L-EPCs) and mesenchymal stem cells (L-MSCs).

Table 1 Human lung resident stem/progenitor cells

Cell type	Cell markers
Tracheal basal epithelial cells	$NGFR^+/ITGA6^+$
Type II alveolar cells	$HTII\text{-}280^+$
Airway epithelial cells	$CD151^+/TF^+$
Airway epithelial cells	$SP/CD45^-$
Lung epithelial cells	$c\text{-}kit^+$ (CD117)
Lung epithelial cells	$Ecad/Lgr6^+$
L-MSCs	$CD73^+/CD90^+/CD105^+$

L-MSC: Lung mesenchymal stem cells.

Epithelial stem/progenitor cells

Certain cells, which were formerly considered to be differentiated airway or alveolar epithelial cells, have been proved to be able to proliferate and differentiate into other lung epithelial cell types under specific conditions, which suggested that they could be adult lung resident stem/progenitor cells. However, characterization and classification of such cells into a hierarchy could be quite challenging since the terms "stem" and "progenitor" are often used interchangeably[6,7]. Moreover, data describing putative populations of human adult resident epithelial stem/progenitor cells are limited compared with the large body of evidence in animal models. Several cellular markers have been used alone or in various combinations to identify and isolate stem/progenitor cells in adult human lung.

The first to identify airway epithelial basal cells having stem cell properties in human adult lungs was a group of French scientists in 2007[8].

By using fluorescence-activated cell sorting, Hajj and collaborators demonstrated that epithelial basal cells, which resided on human adult airway surface and expressed CD151 and tissue factor were able to generate a fully differentiated mucocilliary and functional airway epithelium both *in vitro* and *in vivo*, while maintaining their self-renewal potential.

One year later, the existence of a resident side population (SP) cells within the human tracheobronchial epithelium was demonstrated for the first time[9]. SP cells were identified by verapamil-sensitive efflux of the DNA-binding dye Hoechst 33342. Within SP fraction, $CD45^-$ cells represented 0.12% ± 0.01% of the total epithelial cell population in normal airway. Their epithelial phenotype was confirmed by positive immunohistochemical staining for the epithelial markers cytokeratin-5, E-cadherin, tight junction protein ZO-1 and transcription factor Trp-63 (p63) - mainly isoform ΔNp63. In culture, these cells demonstrated sustained colony-forming and clonogenic capacity as well as well-preserved telomere length over successive passages. Moreover, $CD45^-$ SP cells were able to generate a multilayered differentiated epithelium in air-liquid interface culture, endorsing their stem cell capacity.

Shortly after, tracheal basal cells have been isolated based on their expression of the markers nerve growth factor receptor (NGFR) and integrin α6 (ITGA6)[10]. When cultured under appropriate conditions, $NGFR^+$/$ITGA6^+$ cells gave rise to three-dimensional aggregates (bronchospheres) containing cells positive for transcription factor Trp-63 and cytokeratin 14 (Krt14), luminal cells ($Krt8^+$) and also ciliated cells. Hence, human basal cells have been proved to be capable of both self-renewal and generation of differentiated progenies.

In a recent study, Barkauskas *et al*[11] isolated human type Ⅱ alveolar cells (AT2) using florescence-activated cell sorting based on a biomarker specific to the apical surface of their membrane (HTII-280). When cocultured with fetal human lung fibroblasts, AT2 cells also formed self-renewing three-dimensional colonies (alveolospheres) composed of a single epithelial layer of $HTII\text{-}280^+$ cells.

A putative population of $c\text{-}kit^+$ human lung stem cells nested in niches in the adult distal airways has been identified and characterized as self-renewing, clonogenic, and multipotent both *in vitro* and *in vivo*. When transplanted into damaged mouse lungs, human $c\text{-}kit^+$ cells not only engrafted, but they were also able to generate human bronchioles, alveoli, and pulmonary vessels structurally and functionally integrated with the host organism[12]. As appealing as this hypothesis appears - one adult lung cell being capable to give birth to smooth muscle, vasculature, airways and alveoli - it needs further supporting evidence and validation using lineage-tracing during homeostasis and injury[13].

Shortly after description of c-kit+ human lung stem cells, the existence of another population of putative stem cells was reported[14]. These cells were characterized as positive for E-Cadherin and leucine-rich repeat-containing G-protein-coupled receptor 6 (E-Cad/$Lgr6^+$) while being a sub-population of $ITGA6^+$ cells. In culture, clonally derived E-Cad/$Lgr6^+$ cells formed aggregates capable of *in vitro* indefinite expansion while expressing lung-specific (pulmonary-associated surfactant protein C, Clara cell 10 protein, aquaporin 5), epithelial (E-Cad) and stem cell (Sox9, Lgr5/6, ITGA6) markers. Unlike $c\text{-}kit^+$ cells, E-Cad/$Lgr6^+$ were not able to differentiate into mesenchymal or endothelial cells. E-Cad/Lgr6+ single cell transplantations into the kidney capsule generated differentiated bronchioalveolar tissue while retaining the ability to self-renew[14].

Thus, all these data support the involvement of resident lung stem/progenitor cells in tissue homeostasis, but also in tissue repair after cellular injury.

L-MSCs

Several groups have identified human lung resident cells fulfilling criteria for definition of mesenchymal stem cells[15-18]. According to Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy criteria, the definition of human MSCs comprises: (1) plastic adherence in standard culture conditions; (2) expression of surface molecules CD73, CD90 and CD105 in the absence of CD34, CD45, HLA-DR, CD14 or CD11b, CD79a, or CD19 surface molecules as assessed by fluorescence-activated cell sorter analysis and (3) a capacity for differentiation into osteoblasts, adipocytes, and chondroblasts *in vitro*[19]. Besides these established and generally accepted criteria, another marker which was used to identify human L-MSCs was the ATP binding cassette G transporter[20].

It is common knowledge that mesenchymal stem cells (MSCs) exhibit high telomerase activity and an extensive secretome that is immunomodulatory, antifibrotic, and trophic for endogenous tissue progenitor cells; this robust evidence supports their role as key players in organ homeostasis and repair following injury, and endorse MSCs as ideal candidates for cell-based therapies. L-MSCs demonstrated characteristics similar to other tissue MSCs including paracrine anti-inflammatory properties, suppression of T cell proliferation as well as the ability to differentiate to myofibroblasts[15,21].

Studies conducted so far - both in animal and human lung tissue - identified MSCs niches colocalized with the alveolar capillary network in the distal lung, suggesting that L-MSCs are anatomically similar to adult angioblasts, pericytes and endothelial precursors[22,23]. The data regarding the perivascular location of L-MSCs are in agreement with previously reported information which indicates that the distribution of MSCs throughout the post-natal organism is related to their existence in a perivascular niche[24-26].

Postnatal endothelial progenitor cells

It represent a heterogeneous group of precursor cells, which have been isolated from bone marrow, peripheral and umbilical cord blood, as well as vascular wall, participating in both new blood vessel formation and vascular homeostasis[27-31].

Unfortunately, no specific marker for endothelial progenitor cells (EPCs) has been identified yet. Cells considered being EPCs share distinguishing features as high capacity for self-renewal and regeneration, fast proliferating endothelial colony-forming units and angiogenic properties. The quest for identifying tissue resident EPCs has not been an easy one since the difficulty to discriminate circulating EPCs from bone marrow and tissue resident EPCs.

Currently, the existence of similar cells in the lungs - resident lung EPCs (L-EPCs) - has been highlighted only in animal models. L-EPCs express classical endothelial cell markers (CD31) and display a microvascular phenotype. Furthermore, similarly to circulating and vessel wall-derived EPCs, mouse L-EPCs express CD34, CD133 and VEGFR-2, while rat L-EPCs are negative for CD133. These cells proved to be highly proliferative and capable of renewing the entire hierarchy of endothelial cell growth potentials. Also, L-EPCs are vasculogenic in Matrigel assays *in vitro* and *in vivo*[32-34]. These data support the premise that the lung microvasculature is a rich endothelial progenitor niche, with essential role in maintaining vascular homeostasis.

CIRCULATING STEM/PROGENITOR CELLS

To this point, mainly two circulating stem/progenitor cell types are envisaged as having a potential for immediate clinical application in relation to OSAS: EPCs and MSCs[35].

Circulating EPCs

As previously mentioned, circulating EPCs are bone marrow derived cells that can be found in peripheral and umbilical cord blood.

The phenotype of an accurate EPC, the reliable methods to assess EPCs' quantity and quality as well as their functional status are still under debate. In a review published in 2005, Khakoo *et al*[31] described the EPCs having the following characteristics: (1) they are circulating, bone marrow-derived cells that are functionally and phenotypically distinct from mature endothelial cells; (2) they can differentiate into endothelial cells *in vitro*, as assessed by expression profiles and functional characteristics and (3) they can contribute to *in vivo* vasculogenesis and/or vascular homeostasis.

However, since their first mention[27], the definition of EPCs has come under serious dispute, taking into consideration that further studies have shown that the term "EPC" do not define a single cell type, but rather describe various cell types able to differentiate into the endothelial lineage[36-40].

According to the timing of their growth in culture, there are at least two morphologically and functionally different endothelial cell populations that originate from circulating mononuclear cells: The so-called "early" and "late" EPCs. The early EPCs are derived from the monocytes and express hematopoietic markers such as CD45, CD14, CD11b and CD11c, while the late EPCs, which are believed to be a subset of $CD14^-$ $CD34^-$ KDR^- cells do not express CD45 or CD14. Although these two types of cells are different-originated with distinct function *in vitro*, both of them contribute to *in vivo* neovascularization in animal models of ischemia[41-43].

The existence of two different EPCs populations in human peripheral blood, one with high proliferative capacity and the other with lower proliferative capacity, both with comparable efficacy in neovascularization in an ischemic limb model was demonstrated also by the work of Hur *et al*[44]. Early EPCs had spindle shape, their growth in culture peaked at 2 to 3 wk and died at 4 wk, whereas late EPCs with cobblestone shape appeared after 2 to 3 wk in culture, showed exponential growth at 4 to 8 wk, and lived up to 12 wk. Late EPCs was different from early EPCs, having strong expression of VE-cadherin, Flt-1, KDR, and vWF. Late EPCs produced more nitric oxide, incorporated more readily into human umbilical vein endothelial cells monolayer, and formed capillary tubes better than early EPCs. However, early EPCs had a more pronounced *in vitro* capacity to secrete angiogenic cytokines [such as and vascular endothelial growth factor (VEGF), IL8] in comparison to late EPCs.

The final touch in the field (till this moment) was added by Sieveking and collaborators, who emphasized the "strikingly different angiogenic properties of different EPCs: Late-outgrowth endothelial cells directly participate in tubulogenesis, whereas early EPCs augment angiogenesis in a paracrine fashion, with implications for optimizing cell therapies for neovascularisation"[45]. As for surface markers, their results are consistent with the previous studies, endothelial antigens (*e.g.,* CD31, CD146, VEGFR-2) being expressed by both early and late EPCs. These two populations could be discriminated by CD14 and CD45 expression, with early EPCs showing high expression of these markers (over 95%) whereas late EPCs did not express either maker.

EPCs are able to migrate to the site of injury and participate directly and indirectly to the development of new blood vessels, therefore having a key role in the maintenance of endothelium integrity and function[46]. Moreover, these cells play an essential role not only in physiological neovascularization, but also in pathological conditions (wound healing, tissue regeneration in ischemia, tissue remodeling in diabetes mellitus and heart failure, growth of tumors)[47-50]. Studies conducted so far have shown that EPCs' mobilization from the bone marrow is governed by a multifaceted interaction between cytokines/chemokines, proteinases and cell adhesion molecules[51-55], many of them having abnormal expression in OSAS[56-58].

In order to minimize the potential interfering factors, studies on EPCs in OSAS have been conducted on subjects free of any other known cardiovascular risk factors. OSAS patients and healthy controls were well-matched for age, sex and body mass index; moreover, they had similar blood pressure, fasting blood glucose and total cholesterol levels[59].

Even though, the cumulative results regarding the level of circulating EPCs in OSAS are still under debate, since existing studies have reported heterogeneous data (Table 2).

Five studies out of 11 reported a decrease in EPCs in OSAS patients comparative with healthy controls, either adults or children[60-64]. In contrast with these findings, data from quite similar studies showed that patients suffering of this medical condition had unchanged[65-67] or even increased number of circulating EPCs in peripheral blood compared with the control group[68-70].

It is only natural to ask ourselves why there is so much divergence in apparently similar studies. Some possible reasons concerning this heterogeneity have been identified[59]: (1) Different studies measured circulating EPCs by means of different methods: Flow cytometry *vs* endothelial colony forming units assay; (2) Different investigators used different marker combinations for the assessment of EPCs (Table 2); (3) Different participants: Adults *vs* children or male *vs* men and women; (4) Small number of subjects enrolled, as

Table 2 Circulating endothelial progenitor cells studies in patients with obstructive sleep apnea syndrome

Ref.	Study design	EPCs phenotype	OSAS effect on EPCs number
de la Peña *et al*[60]	Adults, men, flow cytometry	$CD34^+VEGFR2^+$	Reduced number
Jelic *et al*[61]	Adults, both genders, flow cytometry	$CD34^+CD133^+VEGFR2^+$	Reduced number
Jelic *et al*[62]	Adults, both genders, flow cytometry	$CD34^+CD133^+VEGFR2^+$	Reduced number
Murri *et al*[63]	Adults, both genders, flow cytometry	$CD45^-CD34^+CD133^+VEGFR2^+$	Reduced number
Kheirandish-Gozal *et al*[64]	Children, both genders, flow cytometry	$CD34^+CD133^+VEGFR2^+$	Reduced number
Martin *et al*[65]	Adults, both genders, flow cytometry	$CD34^+CD133^+CD45^{dim}$	Unchanged number
Yun *et al*[66]	Adults, both genders, endothelial colony forming units assay	-	Unchanged number
Simpson *et al*[67]	Adults, men, flow cytometry	$CD34^+KDR^+$ $CD45^-CD34^+KDR^+$	Unchanged number
Kizawa *et al*[68]	Adults, men, flow cytometry	$CD133^+CD34^+CD202b^+CD45^-$	Increased number
Lui *et al*[69]	Adults, both genders, flow cytometry	$CD34^+$	Increased number
Chou *et al*[70]	Adults, both genders, flow cytometry	$CD34^+$	Increased number

EPC: Endothelial progenitor cell; OSAS: Obstructive sleep apnea syndrome.

well as the small number of EPCs circulating in peripheral blood.

Also, taking into consideration the complexity of pathogenic mechanisms involved, it is very possible that - depending upon disease severity and duration - certain mechanisms to prevail.

Potential molecular mechanisms through which OSAS has effects on EPCs were reviewed in the exhaustive work of Wang *et al*[59]. Briefly, intermittent hypoxia and sleep fragmentation which are key features of OSAS act as triggers of oxidative stress, systemic inflammation and sympathetic activation.

While most mechanisms lead to decreased EPCs mobilization and increased cell apoptosis, there are others with stimulating effect as regards mobilization through hypoxia inducible factor 1 (HIF-1) regulatory pathway activation and upregulation of proangiogenic factors including vascular endothelial growth factor, stromal-derived factor-1 and erythropoietin.

But what is the effect of treatment on EPCs? The current gold standard treatment for OSAS is CPAP therapy, which has been demonstrated not only to significantly improve sleep quality, reduce the risk of comorbidities and increase patient quality of life, but also to minimize risks of accidents and injuries[71-74]. By effectively diminishing the intermittent hypoxia episodes, CPAP can prevent the activation of pathogenic mechanism that has been shown to affect EPCs number and function.

As depicted in Table 3, CPAP therapy had opposite consequences on circulating EPCs: Normalization in patients having decreased levels[61-63] - or lessening in patients with high levels[68,70]. One study reported unchanged values before and after treatment[67]. Of course, there is an essential factor to consider when assessing rehabilitation effect: Patients' adherence to prescribed therapy. Adherence to CPAP treatment is still a critical and complex issue, subjected to the influence of a wide array of factors[75-79]. Poor adherence to CPAP is generally acknowledged as a major limiting factor in treating OSAS, with a negative impact on therapeutic success[80-82]. Studies conducted in the 1990s or even recently, revealed that approximately 30%-50% of OSAS patients rejected CPAP immediately, the proportion of noncompliant patients reaching 80% within a year[83-86].

Circulating MSCs

MSCs are located mainly in the bone marrow, but are also found in various tissues and organs. When stimulated by specific signals, these cells are mobilized from their perivascular niche into peripheral blood and home to the target tissues where they contribute to local tissue regeneration and homeostasis[87-90].

There is only little evidence regarding the number and function of circulating MSCs in peripheral blood in OSAS; only 3 studies in animal models[91-93], and a single one in humans, in which circulating MSCs could not be detected, probably because their very low number[94].

In an acute rat model of recurrent airway obstructions mimicking OSAS, Carreras *et al*[91] demonstrated early release of MSCs into circulation, higher mobility, increased adhesion to endothelial cells and enhanced endothelial wound repair in rats subjected to recurrent obstructive apneas (15 s apnea/min for 3 h), as compared to the number observed in control animals under normoxia[93]. In addition, in the group of apneic rats subjected to MSCs intravenous injection, MSCs triggered an early systemic anti-inflammatory response by decreasing levels of interleukin-1 beta (IL-1β)[92]. This property of MSCs has been confirmed in a chronic murine model of OSAS in which atrial fibrosis has been inhibited by the intravenous administration of MSCs as a result of normalization of IL-1β plasma levels[95].

Considering all this data, one of the main benefits of MSCs therapy in OSAS patients could be the local and systemic anti-inflammatory effect. Besides this, exposure to hypoxia upregulates microRNA-486 (miR-486) expression in MSCs resulting in increased production of angiogenic factors (hepatocyte growth factor and VEGF), increased proliferation and reduced apoptosis[96].

One of the challenges for cell therapy is that it requires high numbers and good quality of stem cells.

Table 3 Circulating endothelial progenitor cells studies in patients with obstructive sleep apnea syndrome treated by continuous positive airway pressure

Ref.	Study design	EPCs phenotype	CPAP effect on EPCs number
Jelic *et al*[61]	Adults, both genders, flow cytometry	$CD34^+CD133^+VEGFR2^+$	Normalized after 4 wk of CPAP
Jelic *et al*[62]	Adults, both genders, flow cytometry	$CD34^+CD133^+VEGFR2^+$	Normalized after 4 wk of CPAP
Murri *et al*[63]	Adults, both genders, flow cytometry	$CD45^-CD34^+CD133^+VEGFR2^+$	Values returned to control values after 1 mo of CPAP
Simpson *et al*[67]	Adults, men, flow cytometry	$CD34^+KDR^+$ $CD34^+KDR^+CD45^-$	Unchanged
Kizawa *et al*[68]	Adults, men, flow cytometry	$CD133^+CD34^+CD202b^+CD45^-$	Values decreased after 12 wk of CPAP treatment
Chou *et al*[70]	Adults, both genders, flow cytometry	$CD34^+$	Mobilization ratio in patients with OSAS tended to decline

EPC: Endothelial progenitor cell; OSAS: Obstructive sleep apnea syndrome; CPAP: Continuous positive airway pressure.

Among factors impairing the quantity and quality of autologous MSCs is age which is associated with progressive loss of cell proliferation and differentiation potential.

Nevertheless, MSCs cultured under hypoxic condition exhibited enriched self-renewing and proliferation capacity even in aged donors compared to normal condition. It was shown that, at low O_2 concentration (such as 1% O_2) MSCs are resistant to apoptosis and do not lose their beneficial paracrine activity, suggesting that they could be transplanted in hypoxia affected tissues without losing their viability or therapeutic properties[97]. In a very recent study, different profiles of hypoxia-inducible miRNA signatures between young and aged MSCs have been identified and demonstrated to target transcriptional activity leading to enhanced cell proliferation and migration, but also to decrease in growth arrest and apoptosis through the activation of multiple signaling pathways. According to donor's age and culture conditions a therapeutic potential hierarchy of MSCs was established as follows: Young (hypoxia) > young (normoxia) > old aged (hypoxia) > old aged (normoxia)[98].

Another particular aspect concerning MSCs therapeutic applications is related to their hypoimmunogenic or "immune privileged" status; this unique feature endorses them as suitable candidates for allogeneic transplant.

Human MSCs display low levels of human leukocyte antigen (HLA) major histocompatibility complex class Ⅰ, lack major histocompatibility complex class Ⅱ expression and do not express costimulatory molecules CD40, CD80 and CD86[99-101]. Furthermore, these cells have been shown to have immunomodulatory effects on both the innate and adaptive immune system, being able to suppress the activity of a variety of immune cells, including natural killer T cells, dendritic cells, neutrophils, monocytes, macrophages, B and T cells[102-105].

PERSPECTIVES

Research regarding the role of SC in OSAS pathology and their potential use in OSAS treatment is still recent and quite limited, requiring further studies in both animal models and humans. Future directions and recommendations to achieve advanced understanding of mechanisms of lung homeostasis and repair have been proposed during expert meetings[106-108]. In this regard, it is necessary to identify additional cell surface markers to characterize lung cell populations but also to refine the nomenclature used for resident and circulating lung stem cells. Additional studies are required to identify and characterize resident lung stem/progenitors cells and their niches comparatively between different lung compartments and also regulatory pathways guiding their behavior. Mechanisms of recruitment, mobilization and homing of circulating or transplanted cells to various lung compartments have to be elucidated based on disease-specific models (including large animal models).

Maybe the most important take - home messages are those emphasizing the requisite for inter-institutional, multi-disciplinary research collaborations and consortiums. A successful stem cell research requires state-of-the art infrastructure and vast resources. Connecting with existing networks, nonprofit respiratory disease foundations and industry could accelerate clinical applications. Also, joining other clinical trials in related disciplines (*e.g.,* cardiovascular disease) would provide valuable data for development of stem cell research-derived therapeutics.

Last but not least, obtained information must be largely disseminated through existing core services, facilities and web links.

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