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The Implications of Stem Cell Applications for Diseases of the Respiratory System

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Abstract Stem cells possess the unique properties of unlimited self-renewal capability and a broad differentiation spectrum to produce multiple different cell types. This provides many platforms to explore novel multidisciplinary approaches to create and/or restore functional three-dimensional tissues or organs for the treatment of a range of diseases. In this chapter, in the context of respiratory diseases, we review the unique properties of stem cells, and how they have been studied for their therapeutic potential in cell therapy and tissue engineering. In addition, we give a brief overview of the current clinical studies on the use of stem cells for both acute and chronic respiratory diseases.

Keywords Stem cells · Induced pluripotent stem cells · Embryonic stem cells · Adult progenitor cells · Celltherapy · Respiratory diseases

Abbreviations

hESCs	Human embryonic stem cells
ASCs	Adult stem cells
MSCs	Mesenchymal stem cells
iPSCs	Induced pluripotent stem cells
BMNCs	Bone marrow mononuclear cells
EPCs	Epithelial progenitor cells
COPD	Chronic obstructive pulmonary disease
PH	Pulmonary hypertension
IPAH	Idiopathic pulmonary arterial hypertension
RILI	Radiation-induced lung injury

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1 Introduction

Respiratory diseases are a major cause of mortality and morbidity. It has been estimated that more than 1 billion people suffer from chronic respiratory diseases worldwide, with approximately 4 million deaths occurring every year. It is expected that by 2030, chronic respiratory disease will become the third leading cause of death in the world [1].

There is a need for novel therapeutic strategies for the treatment of chronic and acute lung diseases such as lung cancer, pulmonary hypertension, chronic obstructive pulmonary disease (COPD), and asthma because their current treatment options are limited and are mainly aimed at controlling or delaying the progression of the disease. The only plausible option with curative intent would be organ transplantation. However, organ transplantation has its limitations: shortage of donor organs, as well as the life-long need for immunosuppressant therapy after transplantation.

This chapter reviews the promising field of regenerative medicine for respiratory diseases. There are two different ways that regenerative medicine can be applied: (1) it can be a multidisciplinary approach to create and/or restore functional three-dimensional tissues or organs that utilizes a complex combination of stem cells (SCs), scaffolds, and signaling molecules (tissue engineering), or (2) direct application of SCs to the site of injury (cell therapy). In recent years, novel approaches to the treatment of previously incurable diseases by repairing, replacing, or regenerating damaged tissues or organs using SCs have been extensively studied. Hence, the focus of stem cell research is to elucidate their potential for specific diseases and explore methods of controlling differentiation into specific progenitor cells such as endothelial progenitor cells, neural crest cells, or differentiated cell types including type II pneumocytes, cardiomyocytes, and

Table 1 Comparative analysis of different types of stem cells

	Cell sources		
	ESCs	iPSCs	Progenitor cells
Cell characteristics			
Cell of origin	Embryonic	Adult	Adult
Potency	Pluripotent	Pluripotent	Multipotent
Differentiation potential	Unlimited	Unlimited	Limited
Self-renewal	Unlimited	Unlimited	Limited
Karyotype	Stable	Stable	Stable
Homogeneity	Low	Low	High
Immunogenicity	High	Undefined	Low
Limitations			
Technical difficulty	High	Low	Low
Risk of teratoma formation	High	High	Low
Risk of infectious disease	No	Yes	No
Ethical issues	High	Low	Low
Logistical issues	High	Low	Low
Therapeutic benefits			
Cell therapy	Allogenic	Autologous	Autologous
Gene modification	No	Yes	No
Immunomodulation	Undefined	Undefined	Yes

neuronal cells. Stem cells can be applied by direct administration, namely cell therapy or by combining SCs with different components via tissue engineering. If successful, stem cell applications can potentially provide a successful alternative therapeutic option for acute and chronic respiratory diseases.

2 Cell Therapy

Cell therapy (using local or systemic administration) is a well-recognized treatment modality, for example, hematopoietic stem cell transplants for leukemia and epithelial stem cell-based treatments for burns and corneal disorders. The advantages are:

1. Cells can be isolated, expanded, frozen (banked), and retrieved when needed. This enables cells to be harvested before degeneration occurs.
2. Cells can be quality controlled by screening for the presence of pathogens. This ensures safe application for future use.
3. Cells are receptive to gene modification by DNA recombinant technology, for example, gene therapy. This provides the added benefit of genetic manipulation of cells when required.
4. Site-specific cell transplantation can also increase the efficacy and safety of therapy by localized delivery of therapeutic substances at the target site. This would reduce toxicity as a lower dose of cells can be administered directly and be contained at the site of a lesion. In addition, implanted cells can release

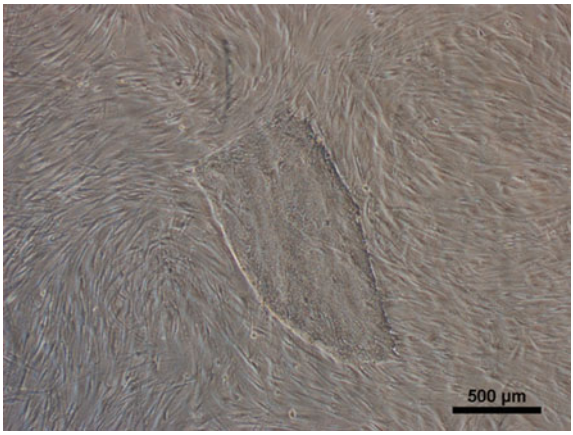

Fig. 1 Human embryonic stem cells (HESCs) on gamma-irradiated human fibroblasts

therapeutic substances at an adaptive dynamic rate determined by the cellular feedback mechanism, which prevents inappropriate dosages.

Nevertheless, cell therapy has its challenges. The ability to achieve cell homogeneity, ensure cell survival and engraftment efficiency, and maintain low immunogenicity during local or systemic administration of cells varies with the type of SCs used. Hence, it is important to discuss the benefits and clinical risks of utilizing different sources of SCs, that is, embryonic stem cells (ESCs), adult stem cells (ASCs), progenitor cells, or genetically modified cells, that is, induced pluripotent stem cells (iPSCs; Table 1).

2.1 Human Embryonic Stem Cells

Human embryonic stem cells (hESCs) can be derived from the inner cell mass of possibly discarded, day 5 healthy, nontransferred embryos (Fig. 1). hESCs have the advantage of being the most therapeutically versatile source of cells. They can proliferate indefinitely to generate daughter cells of identical characteristics without senescence (self-renewing) and are able to maintain their ability to differentiate into almost all tissue-specific cell lineages upon receiving appropriate signals (pluripotency) [2].

Recent experimental studies have examined the reparative and engraftment ability of differentiated cells, that is, type II pneumocytes from hESCs in mouse models. Mouse lung injury models using either bleomycin [3] or silica [4] have demonstrated a reduced inflammation and improved lung function following hESC treatment. The successful engraftment of the differentiated cells from hESC at the site of injury suggests that cell therapy can be useful for the treatment of fibrotic lung diseases. Toya and colleagues (2011) have also shown that mesoderm-induced cell aggregates (embryoid bodies) significantly reduced lung inflammation and edema in a mouse sepsis-induced lung injury model [5].

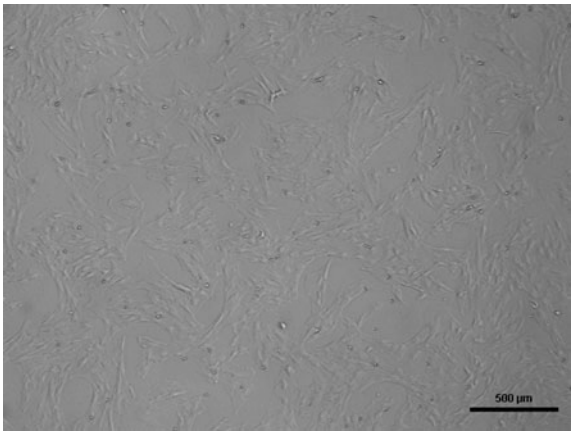

Fig. 2 Mesenchymal stromal cells

Despite the numerous studies that have examined the hESC pluripotency, there are inherent challenges with the use of hESCs: (1) hESCs are derived from an allogenic source and the inability to remove the immunogenic barriers suggests that patients would require long-term immunosuppression; (2) the clinical use of hESCs may be limited by the inability to control differentiation to derive a homogeneous differentiated population of cells; (3) the residing SCs may also pose a risk of teratoma formation in patients; and lastly (4) the use of hESCs in medical research is riddled with ethical and logistical issues because oocytes are needed for ESC isolation. To circumvent these challenges, alternative sources of SCs are required for therapeutic use.

2.2 Adult (Progenitor) Stem Cells

Adult organs set aside reservoirs of stem cells for replenishing cells that are lost in either tissue injury or homeostasis [6]. These stem cells are known as ASCs. ASCs are considered multipotent as they can produce a whole spectrum of cell types within a single cell lineage. They can either be found residing in organs with high cell turnover, such as skin and intestinal tract where the cells' lifespans are measured in days or weeks [7], or in stem cell "factory" organs, that is, adipose tissue and the bone marrow.

In the body, the bone marrow has the largest reservoir of SCs with two distinct residing populations of SCs: hematopoietic and nonhematopoietic. These cells can also be isolated from peripheral and umbilical cord blood. Hematopoietic stem cells (HSCs) can form all blood cells in the body [8] whereas nonhematopoietic stem cells, now known as mesenchymal stromal cells (MSCs) can form cell types mainly associated with skeletal tissue, that is, bone, cartilage, and fat [9].

In recent years, there has been a growing interest in understanding MSCs in terms of their immunomodulatory capability and regenerative potential. MSCs

show many advantages. They are readily available, proliferative, display multilineage potential [10], and are more immune-privileged (Fig. 2). MSCs can release several growth factors and anti-inflammatory cytokines, which regulate endothelial and epithelial permeability and reduce the severity of inflammation.

Numerous experimental studies have explored the effects of MSC therapy in the context of acute lung injury and chronic lung disorders, that is, asthma and COPD. Pati and colleagues (2011) showed in a rat hemorrhagic shock-induced acute lung injury model that human bone marrow-derived MSCs suppress lung edema and inflammatory cells [11]. Sun and colleagues (2011) demonstrated that the intravenous administration of autologous adipose-derived MSCs could attenuate the inflammatory response and oxidative stress in an acute rat ischemia–reperfusion lung injury model [12]. In experiments using asthma as a model for chronic lung disease, it was shown that the decline in lung function was inhibited by rat bone marrow MSCs [13, 14]. This was achieved by reducing airway hyperactivity, inflammation, and remodeling. These murine experimental studies clearly highlight the immunomodulatory role of MSCs. Ingenito and colleagues (2011) on the other hand have demonstrated the regenerative properties of MSCs in an experimental emphysema sheep model [10]. They showed that transplantation of autologous lung-derived MSCs attached to scaffolds induced the regeneration of functional lung tissue in emphysematous regions of the lungs. From these studies, there is compelling evidence that MSCs have beneficial effects on lung development, repair, and remodeling.

Although the use of human MSCs has been successfully used in several cases, there are still hurdles that scientists and clinicians must overcome before incorporating MSC transplantation into routine clinical practice. The invasive procedures on the patient, the low MSC levels present in the marrow (approximately 1 in 100,000 to 500,000 cells), diminished expansion and differentiation ability, the resistance to trypsinization during passaging in vitro, morphological changes in culture, and the requirement of serum-containing media are some of the problems faced with the clinical use of MSCs [8, 15].

2.3 Induced Pluripotent Stem Cells

One potential source of alternative cell types for transplantation is SCs derived from cell reprogramming. Cell reprogramming is described as resetting the developmental clock [16]. It is a process that reverts the genetic status in a somatic cell nucleus to a state of developmental pluripotency to produce an autologous multipotent population of cells [17]. This would potentially be the best solution for cell therapy.

In 2006, Takahashi and Yamanaka developed a novel strategy to derive pluripotent cells from somatic cells called direct reprogramming [18]. iPSCs were successfully derived from both mouse and human somatic cells by ectopic retroviral or lentiviral expression [19] with four transcription factors. The overall estimated efficiency of establishing iPSCs from somatic cells was reported to be less than 0.1 % [18, 20]. However, iPSCs exhibited the essential characteristics of

ESCs: normal karyotype, ESC-like morphology, express cell surface markers and genes that characterize ESC, teratoma formation that showed contribution to all three germ layers (i.e., endoderm, mesoderm, ectoderm), and the contribution to viable chimeras. Numerous studies have suggested that iPSC are almost ESC-like and have a significantly lower level of immunological and ethical concern as compared to ESCs. There are still many ongoing refinements for the method of generating iPSCs. Although Takahashi and Yamanaka (2006) have demonstrated that iPSCs generation is simple, the use of the retroviral reprogramming system may not be safe because the somatic cells could be at risk of permanent genetic alteration and the retroviral vectors could become reactivated. There are other approaches that were explored and the aim of the different methodologies allows one to understand the homing mechanism: this includes cell survival, proliferation, differentiation, and reprogramming.

It is clear from the current literature that the different methodologies of generating iPSCs have demonstrated a successful upregulation of the expression of specific pluripotency genes without transferring potentially harmful genes into the somatic genome. However, despite all the similarities reported between iPSCs and ESCs, microarray gene expression data have been reported to show differences between the two stem cell groups. When these data were reanalyzed in seven different laboratories, it was revealed that nearly one-third of the genes with lab-specific expression signatures were differently expressed between ESCs and iPSCs. This suggests that the ESCs and iPSCs gene expressions differ and the in vitro microenvironment may partially contribute to these differences [21]. Another common problem with the different reprogramming strategies is the extremely low reprogramming efficiencies, ranging from less than 0.0001 % to 0.001 % [22, 23]. The low frequency of reprogramming may be attributed to one or more of these possibilities: (1) the heterogeneous fibroblast population could prevent a subpopulation of cells from reprogramming (2) a small minority population of primitive multipotent cells rather than fully differentiated cells may actually be the source of reprogrammed cells, and (3) the retro- or lentivirus integration used to deliver the reprogramming factors may have modified a small fraction of cells [24].

It is certainly very attractive to know that iPSCs can offer a promising platform for generating patient-specific SCs of any lineage without the need for embryonic materials. Studies performed on endotoxin-induced acute lung injury (ALI) in rodents have also shown that the intravenous delivery of iPSCs can provide a beneficial effect to attenuate the severity of ALI and improve the physiological impairment, which is partly attributed to NF-kB and neutrophil accumulation [25, 26].

3 Tissue Engineering

The goals of tissue engineering are to repair, regenerate, and replace diseased or dysfunctional tissue to restore organ function. Tissue engineering can be conducted either in vivo or ex vivo. In vivo tissue engineering involves the body's

own regenerative capability to generate cells on an appropriate biomaterial. The ex vivo technique involves culturing cells on a scaffold and reimplanting it into the host [27].

In scaffold-based tissue engineering, there are a number of important factors to consider: route of delivery, pre-conditioning using different growth factors or cytokines, immunological function, and accessibility and availability of cell sources. Cells may be allogeneic (same species, different individual) or autologous (same individual) [28]. Although autologous cells are preferred because an immunologic response is not evoked, there might be problems with achieving an adequate cell yield for expansion and transplantation, especially in patients with end-stage organ disease. Furthermore, some primary autologous human cells cannot be expanded from particular organs (i.e., brain, pancreas, and lung).

4 Clinical Applications of Cell Therapy

Animal models have been used to examine its engraftment during transplantation and airway reconstitution in animal models with experimentally induced tracheal and lung defects. Current trends in tracheal and lung transplantation include the use of autologous cells, development of bioactive cell-free scaffolds that are capable of supporting activation, and differentiation of host SCs at the site of injury.

4.1 Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease that is characterized by a progressive airflow limitation that is not fully reversible. Cigarette smoking is one of the most common risk factors in COPD although inhalational exposures to certain occupational dusts and chemicals have also been implicated. A genetic risk factor for COPD is alpha1-antitrypsin deficiency.

Small airway disease and lung parenchymal destruction are two components that contribute to airflow limitation, and these are caused by an abnormally amplified inflammatory response of the lungs to noxious particles and gases. An increased level of pro-inflammatory mediators and oxidative stress in the respiratory tract characterizes this inflammatory response. This results in airflow limitation and air trapping (small airway disease). It also impairs gaseous exchange, causes mucus hypersecretion, and parenchymal destruction [26, 29–31].

Several animal models have demonstrated that MSCs have its “protective” mechanism towards an inflammatory response [31–33]. To evaluate the immunomodulatory role of MSCs in humans, a clinical trial was carried out on allogenic-derived bone marrow MSCs transfusion to patients with moderate to severe COPD (NCT00683722). The study showed that at 6 months the intravenous

infusion of MSCs significantly reduced the inflammation as measured by C-reactive protein (CRP). No adverse events or increased incidence of infections were seen. This reinforces the immunomodulatory capability of MSCs. However, after 6 months of treatment with MSC, pulmonary function tests were not significantly improved over placebo control, although it did reveal positive trends in functional endpoints such as the six-minute walk test, especially in patients with less severe COPD. Nevertheless, a longer follow-up is necessary to evaluate the MSC efficacy on improving the pulmonary function and quality of life.

Another study with a longer follow-up period of 12 months showed that patients with stage-4 COPD, who underwent stem cell infusion using bone marrow mononuclear cells (BMNCs), reported significant improvement in quality of life. Their clinical condition also stabilized, which can be inferred that the natural progression of the disease was altered. More important, no adverse events were reported (NCT01110252). Nevertheless this study had a small sample size of four patients, but has been expanded and to date is still ongoing. Studies with a larger sample size and longer follow-up period would be helpful to assess the efficacy of stem cell therapy in COPD patients. To date, there have been no other clinical trials that have utilized stem cell therapy in COPD patients.

4.2 Pulmonary Hypertension

Pulmonary hypertension (PH) is defined as elevated pulmonary arterial pressure (mean pulmonary artery pressure > 25 mmHg at rest) and right ventricular failure. Based on the different mechanisms of PH, the World Health Organization (WHO) has classified it into five groups; pulmonary arterial hypertension, pulmonary hypertension owing to left heart disease, pulmonary hypertension owing to lung diseases or hypoxemia, chronic thromboembolic pulmonary hypertension, and pulmonary hypertension with unclear multifactorial mechanisms [34, 35].

The pathogenesis of PH was studied largely in the context of idiopathic pulmonary arterial hypertension (IPAH), in which vascular endothelial dysfunction appears to be a key element. This dysfunction manifests as a proliferative vasculopathy, characterized by deregulated cell proliferation leading to intimal hyperplasia and smooth muscle hypertrophy, fibrosis, vasoconstriction, and thrombosis. This form of remodeling is a "disordered angiogenesis" process and it increases pulmonary vascular resistance, causing pulmonary hypertension, and with increasing severity leads to right ventricular failure. Hence, IPAH is a slowly progressive disease with poor prognosis, which ultimately leads to death.

Based on the concept of vascular endothelial dysfunction, it has been postulated that endothelial progenitor cells (EPCs) could support angiogenesis via a paracrine mechanism as it was shown to secrete crucial pro-angiogenic factors such as VEGF-A, CXCL12, and insulinlike growth factor-1. Hence, in supporting angiogenesis, EPC promotes repair and reduces the pathological morphology seen in PH. This hypothesis was supported by a number of murine studies [34]. In

addition, because adenoviral overexpression of endothelial nitric oxide synthase (eNOS) in the lung is known to reduce PH, Kanki-Horimoto et al. (2006) showed in a rat study that implanting MSCs that overexpressed eNOS could reduce the effects on PH-related right ventricular impairment and increase survival time [36]. Jungebluth et al. (2011) have also demonstrated the restoration of lung function at a proteomic level in a PH rat model when allogenic MSCs were administered [37].

Based on encouraging pre-clinical data, two clinical trials conducted in Zhejiang University, Hangzhou, China (NCT00257413, NCT00641836) investigated the feasibility, safety, and clinical outcome of intravenous infusion of autologous EPCs in patients with IPAH. This was compared with conventional therapy. At 12 weeks of follow-up, the cell infusion group reported a significant improvement in the six-minute walk distance compared with the conventional therapy group. There was also significant improvement in mean pulmonary artery pressure, pulmonary vascular resistance, and cardiac output. No severe adverse events with cell infusion were reported. In lieu of this, a 12-week clinical trial of autologous EPCs transplantation in an open-label pilot study was conducted, involving 13 pediatric patients with IPAH [38]. The pilot study showed that EPCs intravenous infusion was associated with significant improvements in the six-minute walk distance, New York Heart Association (NYHA) functional class, and pulmonary hemodynamics. No adverse events with cell infusion were reported. The results from the clinical trials suggest EPC infusion has its potential benefits in both adult and pediatric age groups.

In 2005, autologous progenitor cell-based gene therapy of heNOS was intravenously infused in patients with severe IPAH that was refractory to conventional treatment (NCT00469027). This was a landmark trial involving the use of EPCs combined with a therapeutic gene therapy (heNOS) to treat IPAH. To date, the six patients show significant reduction in total pulmonary vascular resistance, and there is no safety concerns reported thus far. Therefore, stem cell applications for IPAH show promising results and may offer an alternative therapeutic solution.

4.3 Radiation-Induced Lung Injury

Radiation-induced lung injury comprises radiation pneumonitis and fibrosis, in which pneumonitis tends to present in the subacute stage whereas fibrosis tends to present late. It is largely observed in patients who have undergone chest wall irradiation for the treatment of lung, breast, and hematological malignancies.

The pathogenesis of radiation-induced lung injury is a combination of radiation-induced cytotoxicity and inflammatory responses. Radiation causes DNA damage resulting in cellular death. It also induces cellular apoptosis. Moreover, radiation is known to upregulate a milieu of inflammatory cytokines (e.g., TGF-beta, TNF-a, IL-1a, IL-6, PDGF, bFGF) [39]. Currently, there are no standard guidelines in the treatment of radiation-induced lung injury. However, the general consensus is the use of glucocorticoids or other immunosuppressants such as

Table 2 Current clinical trials of stem cell therapy in respiratory diseases

Diseases	NCT	Stem cell type	Origin	Mode of administration	Findings
COPD	00683722	BM-MSC	Allogenic	Intravenous	No significant improvement in pulmonary function but possible improvement in functional end points (e.g., 6-minute walk test
	01110252	BM-MNCs	Autologous	Intravenous	Significant improvement in quality of life
IPAH	00257413 00641836	EPCs	Autologous	Intravenous	Significant improvement in mean pulmonary artery pressure, pulmonary vascular resistance, cardiac output, and 6-minute walk distance
	00469027	EPCs + gene therapy (heNOS)	Autologous	Intravenous	Significant improvement in pulmonary vascular resistance
Radiation-induced lung injury	Nil	MNCs	Autologous	Intravenous	No progression of lung injury at 1 year post-treatment

azathioprine and cyclosporine, which appear to benefit in the pneumonitis stage but not at the fibrosis stage. Experimental agents including pentoxifylline and inhibitors of collagen synthesis (e.g., colchicine, penicillamine) were suggested for use in the fibrosis stage, but to date there is still no concrete evidence to support this. Therapeutic effects from stem cell therapy were explored in a rat model and in a pilot clinical trial [40]. It was reported that a single transplantation of autologous MSCs was associated with a decrease in mortality rate in mice that underwent radiation-induced lung injury. The pilot clinical trial also demonstrated that when standard pharmacotherapy was combined with intravenous autologous MSCs administration in 11 patients with radiation-induced lung injury, there was no progression of the lung injury at 1 year post-treatment. This suggests that stem cell therapy can play a role in the treatment of radiation-induced lung injury. However, the results of this clinical trial could be confounded by the use of pharmacotherapy. In addition, prospective placebo controlled trials would be more appropriate to assess the therapeutic effect of SCs accurately.

Table 3 Current clinical trials of tissue engineering in respiratory diseases

	Tissue engineered	Tissue scaffold	Findings
Omori et al.	Trachea	Marlex mesh tube	Good epithelialization to cover the implant
	Larynx	Marlex mesh tube	Good epithelialization and no airway obstruction
Zhang et al.	Pharynx and larynx	Alloderm, ADM	Satisfactory wound healing but some degree of stenosis reported
Macchiarini et al.	Trachea	Decellularized donor trachea	Airway remained vascularized and quality of life improved. At long-term, limited collapse occurred in 30 % of the patients
Jungebluth et al.	Trachea and bronchi	Synthetic micro- and nanofibers	In progress

5 Clinical Applications of SCs in Tissue Engineering

With the ongoing search for SCs that can be applied to human treatment, precise delivery and homing to the disease site must be ensured for successful therapy. SCs were shown in clinical studies to be safely inoculated into the trachea (Table 2). Most tracheal tissue-engineering approaches use biodegradable three-dimensional scaffolds, which are important for neotracheal formation by promoting cell attachment, cell redifferentiation, and production of the extracellular matrix (Table 3). An important milestone in applying regenerative medicine techniques to the respiratory system is using artificial tissue scaffolds to reconstruct organs that could later be used for implantation.

Omori and colleagues (2005) applied this concept by using a tissue scaffold (Marlex mesh tube) and covering it with collagen sponge to form part of a trachea [41]. A two-year follow-up reported that the reconstructed trachea showed good epithelialization to cover the implant with no complications. In view of this success, Omori and colleagues (2008) used the same technique to repair the larynx and trachea in another four patients (one with subglottic stenosis, three with thyroid cancer) [42]. Within 8–34 months follow-up, post-operative endoscopy showed that the lumen of the implants was well epithelialized and no obstruction was observed.

Recently, significant advances were made in the field of tissue bioengineering. Zhang and colleagues (2010) performed a study on patients with hypopharyngeal carcinoma [43]. They used tissue patches made from artificial biological material (i.e., acellular dermal matrix; Alloderm, ADM), combined with pectoralis major myocutaneous flaps (PMMFs), to reconstruct the surgical defect created from total laryngectomy and total hypopharyngectomy. ADM tissue patches were also used to reconstruct the defect in the posterior pharyngeal wall from patients who only underwent tumor resection. This study reported satisfactory wound healing with

good coverage of the defect by the growing epithelium 18–37 days post surgery. There was also no pharyngeal fistula. However, they reported some degree of stenosis in the pharyngeal cavity occurred, but following dilatation of the stenosis, patients could have a regular diet. This study demonstrated that stem cell technology could be incorporated into tissue engineering, to create "biological plasters" that could be used to mend surgical defects.

A major milestone was achieved with the transplantation of the first bioengineered trachea: a combination of SCs and tissue-engineering techniques. In 2008, a bioengineered human trachea was constructed from a human donor trachea and was transplanted to a patient [44]. Its MHC antigens and cells were removed, and the trachea was recolonized with the recipient's epithelial cells and MSC-derived chondrocytes that had been cultured ex vivo. This was surgically transplanted to replace a stenosed left main bronchus in a patient with end-stage bronchomalacia. Post-surgery, the patient did not require immunosuppressants and the blood had no traces of anti-donor antibodies. At 4 months post-surgery, the patient's airway remained functional and quality of life was improved dramatically. This landmark case highlights the tremendous potential of regenerative medicine that combines tissue regeneration techniques using SCs to create functional organs that can be transplanted in humans. It also offers a paradigm shift with the concept that human organ transplantation does not require long-term immunosuppressant therapy to ensure organ viability.

6 Conclusions

In the foreseeable future, stem cell and tissue-engineering technology can offer a therapeutic solution in the treatment of previously incurable and possibly certain genetic, diseases. It has been shown in many animal studies and a few clinical trials to have an immense potential in treating diseases by repairing, replacing, or regenerating tissues and restoring the function of an organ. Nonetheless, the field of regenerative medicine is still in its infancy and continuing research into genomics and bioinformatics technologies will continue to offer new insights into the understanding of SCs growth, differentiation, and their application to engineering tissues in the future.

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