ERS Congress 2024: highlights from the Basic and Translational Sciences Assembly

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In case you missed #ERSCongress 2024, this article highlights the regenerative potential of #stemcells in lung diseases discussed at the @EuroRespSoc Congress. @SaraOcana1 @MariOzaki14 @EarlyCareerERS https://bit.ly/3XZQtNk

Cite this article as: Wang L, Ozaki M, Heijink IH, *et al*. ERS Congress 2024: highlights from the Basic and Translational Sciences Assembly. *ERJ Open Res* 2025; 11: 00147-2025 [DOI: 10.1183/23120541.00147-2025].

Received: 31 Jan 2025
Accepted: 4 April 2025

The 2024 European Respiratory Society (ERS) Congress took place on 7–11 September in Vienna, Austria. Among numerous disease-specific oral presentation sessions, there was a special session on "The regenerative potential of stem cells in lung diseases" to discuss the translational science aspects of stem cells across diseases from a multidisciplinary view [1]. This session and additional stem cell related abstracts presented at the congress are summarised in this article, highlighting the main advances made by each study.

What do we know about resident stem cells?

Resident lung stem and progenitor cells are a heterogeneous group of cells involved in lung tissue regeneration, including epithelial progenitors (*e.g.* basal and club cells in the airways, alveolar type 2 (AT2) cells in distal lungs), endothelial progenitors and lung-resident mesenchymal stem/stromal cells (LMSCs). These cells collectively play essential roles in lung maintenance, repair and regeneration. While not all lung stem/progenitor cells are multipotent, they exhibit varying self-renewal and differentiation capacities to maintain tissue homeostasis, facilitate repair after injury and/or support site-specific epithelial and endothelial proliferation and differentiation/regeneration.

A specialised group of cells called pulmonary capillary endothelial cells (PCECs) play a critical role in alveolar repair. A subset of PCECs known as general capillary (gCap) can self renew and serve as progenitors for both gCap and aerocyte (aCap) cells during alveolar repair. In idiopathic pulmonary fibrosis (IPF) patients, these gCap and aCap capillary cells are lost and are replaced by systemic venous endothelial cells (SVECs). Single-cell RNA sequencing in mice identified new endothelial cell subpopulations: leucine-rich alpha-2-glycoprotein 1 (Lrg1)$^+$ gCap and Lrg1$^+$ aCap. These subpopulations were found only in bleomycin-treated mice and were shown to have pro-angiogenic profiles that are associated with alveolar niche regeneration. These Lrg1$^+$ cells were not found in IPF patients of an examined human dataset; however, the pro-angiogenic signatures were partly reproduced in their SVECs [2].

LMSCs have also been implicated in lung tissue repair in IPF. Beside their regenerative potential and secretion of regenerative factors, LMSCs can contribute to IPF pathogenesis by differentiating into myofibroblasts, with recent transcriptomic data showing that mesenchyme development and collagen metabolism are two distinct biological processes in IPF compared with control-derived LMSCs [3]. A recent study found that although IPF-derived LMSCs do acquire myofibroblastic features *in vitro*

(*e.g.* express extracellular matrix (ECM) proteins and α-smooth muscle actin), they have a lower response to profibrotic stimuli in bleomycin-treated mice compared to control LMSCs. LMSCs appeared to affect bleomycin-induced histology and molecular signs of fibrosis and inflammation, but cytokeratin-8 and -18 protein levels were higher ($p<0.05$) in control LMSC-inoculated mice. Further characterisation of IPF LMSCs showed reduced regenerative activity, mitochondrial dysfunction and changes in the expression of senescence and pro-apoptotic markers. This suggests that IPF LMSCs do not promote lung fibrosis, which may be caused by the exhaustion of stem cells due to accelerated ageing in the LMSCs in IPF [4].

Stem cells interact closely with fibroblasts, which play a crucial role beyond their structural function in producing ECM. Fibroblasts act as hubs, integrating and responding to lung microenvironment changes [5]. Fibroblasts modulate inflammation and regeneration by secreting growth factors, cytokines and chemokines, forming a critical axis with lymphocytes and stem cells to regulate inflammation and regeneration. For example, regulatory T-cell (Treg)-derived amphiregulin has been shown to promote lung epithelial repair through fibroblast signalling [6], while Treg-derived interleukin (IL)-1 receptor antagonist (IL-1Ra) reduces early inflammation by inhibiting IL-1-driven fibroblast activation [7]. Additionally, the loss of fibroblast hedgehog-interacting protein (HHIP), a negative regulator of sonic hedgehog (SHH) signalling, increases the susceptibility to develop emphysematous manifestations [8]. SHH signalling activates fibroblasts, which produce IL-7 to support resident T-lymphocytes (Trls). Deletion of SHH-responsive fibroblasts in mouse models reduces interferon (IFN)-γ^+ Trls, disrupting the T-cell niche in the lung [9]. These insights position fibroblasts as central players in the lung microenvironment, with significant therapeutic potential for respiratory disease treatments [6, 7, 9]. A summary diagram highlighting the role of stem cells in lung repair and regeneration is shown in figure 1.

The therapeutic potential of resident lung stem/progenitor cells has been examined in airway and distal lung diseases. In conditions like epidermolysis bullosa, airway basal cells expressing laminin-332 are promising gene therapy targets. Notably, stent-based epithelial cell delivery, demonstrated through a

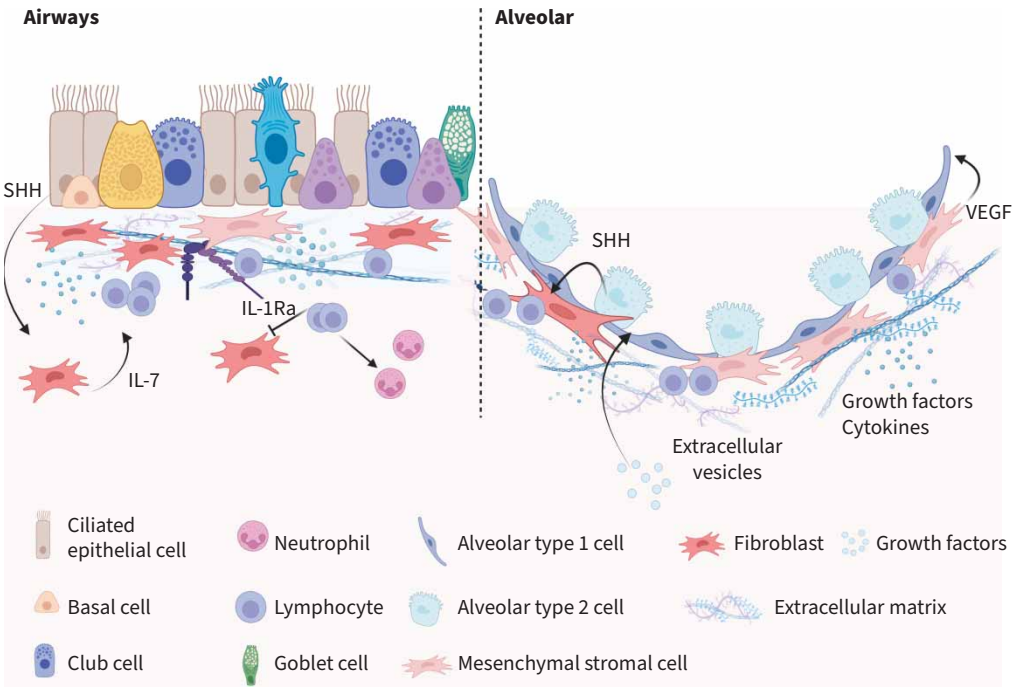

FIGURE 1 Stem cell-mediated signalling and interactions in airway and alveolar regions of the lung microenvironment. This schematic highlights the role of stem cells in lung repair and regeneration. In the airway region (left), epithelial progenitor cells interact with fibroblasts, supported by sonic hedgehog (SHH) signalling. SHH-stimulated fibroblasts produce interleukin (IL)-7, which sustains immune cell populations, while regulatory T-cell-derived IL-1 receptor antagonist (IL-1Ra) modulates fibroblast activity to reduce inflammation. In the alveolar region (right), mesenchymal stromal cells and epithelial progenitors secrete extracellular vesicles, growth factors and cytokines that support alveolar regeneration. SHH signalling and vascular endothelial growth factor (VEGF) further promote angiogenesis and repair.

surgical transplantation model, involving short-segment tracheal resection and primary anastomosis in rabbits, showed encouraging airway restoration results, although the challenge remains in long-term engraftment [10]. Mesenchymal stromal cells (MSCs) have been used in clinical trials for acute respiratory distress syndrome (ARDS) treatment, but patient response varies due to differing inflammatory environments. MSC licensing, where MSCs adapt to inflammatory conditions, is crucial for efficacy, especially as ARDS patients show both hypo- and hyper-inflammatory phenotypes, even though hyper- and hypo-inflammatory ARDS serum could lower the inflammation profile. Interestingly, MSCs exposed to hyper-inflammatory ARDS serum produce significantly more vascular endothelial growth factor (VEGF), enhancing lung epithelial barrier function, as confirmed in CALU-3 cells and an *in vivo* lipopolysaccharide-induced lung injury model [11]. Preconditioning MSCs with pro-inflammatory cytomix (IL-1β, tumour necrosis factor (TNF)-α, IFN-γ) boosts their viability, and immunomodulatory and antimicrobial properties [12], indicating that these cells may become activated in an inflammatory environment, while physiomimetic lung ECM-derived hydrogels significantly enhanced extracellular vesicle secretion compared to standard substrates, offering a promising cell-free therapeutic approach. These advancements underscore the need to optimise stem cell therapies for personalised treatments in airway and lung repair [13].

Potential use of induced pluripotent stem cell-based models

Rodent lung models and *in vitro* models using primary lung cells have advanced many aspects of lung disease research. However, primary lung cells are difficult to obtain and often change phenotype under *in vitro* cell culture conditions, while species differences limit the clinical relevance of rodent lung models. Instead, human induced pluripotent stem cells (hiPSCs) provide a highly appealing *in vitro* model to study lung disease that can help us investigate the role of the cellular components in lung diseases, as they can be generated in large quantities from accessible sources, shared, stored, gene-edited and differentiated into various cell types. hiPSCs have been used to model numerous lung diseases including COPD, interstitial lung disease, alpha-1 antitrypsin deficiency and cystic fibrosis.

A recent study engrafted anterior foregut endoderm cells derived from the hiPSCs of COPD patients onto a mechanically injured air–liquid interface differentiated human epithelium and found that wound closure was more rapid in the epithelium treated with the graft, and that basal and ciliated cells were detected at 42 days post graft [14].

Other recently developed hiPSC models include the first *in vitro* severe asthma human model recapitulating epithelium cell remodelling, severe asthma heterogeneity, and the mucus plugging endotype [15]. In addition, an *in vitro* hiPSC-derived AT2 model generated from patients with short telomere gene mutation-related familial pulmonary fibrosis can help investigate the molecular role of telomere-related genes in pulmonary fibrosis [16].

Additionally, gene editing hiPSCs followed by tissue-specific differentiation provides a complementary platform to interrogate the effects of genetics on respiratory diseases. However, gene editing of hiPSCs can be highly challenging, time consuming and expensive, usually achieving low editing efficiencies. In light of this, a recent study showed that both human embryonic stem cells and hiPSCs can be gene-edited with up to 10% editing efficiency, using TALENs and CRISPR-Cas9, resulting in a robust and reproducible method that enables the generation of gene-edited iPSCs in <1 month [17, 18].

Novel therapeutic approaches

The rapidly evolving field of stem cell technologies brings new opportunities for the use of stem cells in future therapeutics. Recently, $P63^+$ lung progenitor cells, which serve as airway epithelial progenitors but also participate in alveolar repair and regeneration, have been used for both COPD and IPF therapy. Phase I clinical trials, whereby autologous $P63^+$ lung progenitor cells derived from bronchial brushings were expanded *in vitro* and were transplanted back into the patient, showed significantly improved lung function in both COPD and IPF patients [19]. This cell-based therapeutic strategy has now been approved for phase II clinical trials for COPD and IPF in China [20].

Novel therapeutic approaches are emerging using MSC-derived exosomes. Nebulised umbilical cord MSC-derived exosomes significantly improved lung function, restored alveolar morphology and reduced mortality in a bleomycin-induced pulmonary fibrosis mouse model. Aerosolised exosome delivery offers a noninvasive method to enhance target site concentration and therapeutic efficacy [21], overcoming the rapid clearance challenge associated with MSCs in clinical trials.

Haematopoietic stem cell transplantation (HSCT) offers potential curative benefits for paediatric conditions, but it presents challenges, particularly in identifying pulmonary complications and managing conditioning-related toxicity [22]. Pulmonary complications such as graft-*versus*-host disease (GVHD) are relatively common in patients who have undergone HSCT; thus, it is essential to carefully diagnose and treat these patients following a multidisciplinary approach that carefully weighs the risks of other complications. Allogenic HSCT causes multiple risk factors for bronchiectasis and results in symptomatic new-onset bronchiectasis (SNOBE). Patients identified with SNOBE have chronic GVHD with unique characteristics. This indicates the need for early involvement from respiratory specialists [23].

Overall, the high number of stem cell-based studies presented at the ERS Congress 2024 highlights the increasing interest of the field in these cells, to investigate the mechanisms leading to lung diseases, as tools for the study of the contribution of genetic *versus* environmental factors, and as potential treatments for lung conditions.

Provenance: Commissioned article, peer reviewed.

Conflict of interest: L. Wang has nothing to disclose. M. Ozaki reports support for the present manuscript from Research Ireland Awards Starting Laureate Award (IRCLA/2022/1572). I.H. Heijink reports grants from Dutch Lung Foundation, Dutch Scientific Organization (NWO), Roche, Boehringer Ingelheim and AstraZeneca, and declares support from the ERS to attend the ERS Congress 2024 as Head of Assembly 3. S. Cuevas-Ocaña reports receiving support from the ERS to attend ERS Congress 2024 as Early Career Member representative of Assembly 3 and Chair of the Early Career Member Committee.

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