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Chronic airway disease as a disorder of epithelial homeostasis: Mechanistic insights and the emerging role of hiPSC-Derived Airway Models

Ahmed LAZRAQ *

Histology - Embryology - Cyto - Genetics Laboratory, Faculty of Medicine and Pharmacy, Fez. Morocco.

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Abstract

Chronic obstructive pulmonary disease (COPD) is increasingly recognized as a disorder of epithelial instability and defective tissue repair rather than a disease driven solely by chronic inflammation. This review examines the role of airway epithelial homeostasis, regional progenitor cell dysfunction, and impaired regenerative mechanisms in COPD pathogenesis, while highlighting the emerging applications of human induced pluripotent stem cell (hiPSC)-derived airway systems. The airway epithelium functions as an active interface that regulates barrier integrity, immune signaling, mucociliary clearance, and responses to environmental and mechanical stimuli. Disruption of these functions results in persistent epithelial injury, abnormal differentiation, mucus dysregulation, and progressive airway remodeling. Because different regions of the respiratory tract depend on distinct progenitor populations, including basal cells, club cells, and alveolar type II cells, regional impairment of these progenitors contributes to defective repair and disease progression. Recent evidence also suggests that COPD may originate from impaired lung development and early-life susceptibility, with distal airway abnormalities preceding advanced structural damage. hiPSC-derived airway models overcome many limitations of conventional animal models by generating renewable, patient-specific human airway epithelium that faithfully reproduces key developmental and pathological features of COPD. These platforms provide valuable tools for investigating disease mechanisms, testing therapeutic interventions, and advancing regenerative strategies. Although significant translational challenges remain, hiPSC-based airway reconstruction represents a promising approach for future precision medicine and regenerative therapies in COPD.

Keywords: Chronic Obstructive Pulmonary Disease (COPD); Airway Epithelial Homeostasis; Human Induced Pluripotent Stem Cells (hiPSCs); Epithelial Repair and Regeneration; Airway Progenitor Cells

1. Introduction

For a long time, asthma and chronic obstructive pulmonary disease (COPD) were considered as inflammatory disorders, but recently they are rather considered as a disease of epithelial instability and defective repair [1], [2], [3]. The epithelium of airways on the one hand plays the role of a barrier supporting immune signaling, mucociliary clearance, and host defense, on the other hand the stem cell and progenitor populations of respiratory epithelium maintain homeostasis and restore epithelial integrity after injury [1], [2], [4], [5]. Repair failure leads to chronic diseases by many mechanisms such as persistent barrier dysfunction, abnormal differentiation, altered mucosal defense, mucus dysregulation, and progressive remodeling [1], [2], [3].

A fragile epithelium and defective repair lead to inflammation and environmental sensitivity in asthma [3], whereas in COPD the epithelium regeneration is defective, and progenitor cells are lost or exhausted which leads to disease progression. This new approach suggests that chronic pulmonary diseases are the result of epithelial homeostasis imbalance, progenitors' impairment, and defective tissue repair [5], [6].

* Corresponding author: Ahmed LAZRAQ

Human induced pluripotent stem cell (hiPSC)-derived airway systems, allowed a major advance in modeling diseases in real human tissue derived from directed differentiation, which enables a full three-dimensional airway epithelial cells construction [7], [8], [9]. hiPSC-derived airway systems are already utilized in modeling in cystic fibrosis to evaluate treatment response and gene correction, they are even used in modern regenerative therapy [10], [11].

In this review, we explore how abnormal airway epithelial homeostasis, and progenitors' lesions lead to COPD, and how hiPSC-derived airway systems are useful in modeling this pathology and contribute to development of modern restorative therapy.

2. Pulmonary Homeostasis at the Environmental Interface

The lung has its own particularity since it is a deep internal organ hard to access, just like heart; even so, the airway epithelium surface is paradoxally in continuous contact with external environment including allergens, microbes, pollutants, and mechanical forces of ventilation. So, the airway epithelium is not just a physical barrier since the homeostasis of the lung depends on its capacity to act as an active sensor capable of integrating immune, microbial, and biomechanical signals, by maintaining a controlled state of interaction that combines effective defense against pathogenic agents, and limitation of excessive inflammation toward innocuous agents. Any disruption of this balance leads to inappropriate epithelial response affecting barrier integrity, mucus production, and respiratory function [1], [12].

The learning process of airway local immune system begins early in life; this is supported by epidemiological and mechanistical evidences of many studies stating that childhood exposure to rich and diversified antigenic environment improves the immune tolerance of airways [13]. A notable example is given by Stein et al. that found a lower prevalence of asthma in Amish children who live in farming environment compared to Hutterites who live in city, despite being genetically close and having closely related ancestry [14]. This protective effect has been linked to the differential expression of A20 (TNFAIP3) a crucial regulator of immune system and negative regulator of NF-κB-dependent inflammatory signaling which limits allergic sensitization, these observations demonstrate that airway epithelium is not only exposed to environmental conditions but it is also influenced and conditioned by them [1], [15].

Immune system tolerogenic state must be compatible with efficient antimicrobial defense. In healthy lungs, epithelial clearance and local immune system allow generally effective containment and inactivation of inhaled pathogenic agents without excessive immune response [1]. Such is the case of efficient clearance of inhaled Aspergillus fumigatus; and the induction of epithelial innate immunity during colonization at the human mucosal surface by Streptococcus pneumoniae [16], [17].

The airway epithelium undergoes a continuous mechanical stress with each respiratory cycle; it must accommodate with these mechanical forces' variation without injury. This adaptation is possible in physiological conditions through mechanotransduction; however, under extreme conditions this same mechanism can lead to inflammation, barrier disruption, and injury [18]. This is demonstrated in ventilator induced injury, where airway epithelium plays a major role in amplification of inflammatory phenomena when it is exposed to abnormal mechanical forces [19].

Collectively, the airway epithelium is not just a barrier, it is rather a central pulmonary structure capable of performing many important functions by integrating environment tolerance, efficient defense, and accommodating to mechanical stress. Each time this meticulous balance is affected the capacity of regeneration is compromised and chronic inflammatory states become more likely, which is a new perspective for both preventive and regenerative strategies [1], [12], [15], [19].

3. Regional Epithelial Progenitors and Defective Repair in Chronic Respiratory Disease

Defects of airway epithelial repair can be considered as the central mechanism in chronic respiratory diseases. This epithelium is highly regionalized since it differs considerably from segment to the other in respiratory tract, resulting in different regenerative responses from the proximal conducting airways to the distal bronchioles and alveoli [2], [12]. This spatial distribution is the key in comprehension of chronic airways diseases, particularly bronchial epithelium which is found in an intersection of environmental exposure, host defense, inflammatory signaling, and tissue remodeling [3], [20].

The reason behind anatomical difference in regenerative capacity across respiratory tract is that the progenitors in every segment are different, and there is no single universal stem cell able to regenerate all the epithelium [2]. In fact, basal cells are the progenitors of the proximal airway, whereas club cells are the major cellular component responsible

of maintenance and repair in distal conducting airways, and finally type 2 alveolar cells are the main stem cells in alveolar compartment [4], [12], [21]. So, each specific region of respiratory tract relies on specific progenitor/stem cells in the process of its regeneration, repair, and homeostasis [2], [21].

These reparative mechanisms are affected in quantitative and/or qualitative way in chronic diseases; in this case, the progenitors' potential declines and epithelial repair becomes incomplete, and maladaptive remodeling persists. In COPD, this maladaptive response and basal progenitor's exhaustion in epithelium have been documented, which aligns with the broader concept of failed epithelial repair introduced above [2], [6], [22].

Additionally, local microenvironment plays a key role in shaping progenitors' behavior, and all stromal inflammatory and paracrine signals can modulate the survival, lineage choice, and differentiation. For example, it has been demonstrated that IL-6/STAT3 signaling pathway can promote ciliated cells regeneration from basal stem cells, this illustrates that microenvironment contributes alongside with progenitor-intrinsic capacity to successful repair [2], [23].

Thus, chronic airway disease is not just a persistent injury, but also a defect of special organization of repair potential of the lung, which means that region specific progenitors are no longer able to restore epithelium in an appropriate manner. This is particularly relevant to regenerative medicine, since it implies that a comprehensible therapy through the regional reconstruction of affected airways will require restoration of both lineage fidelity and microenvironmental factors [2], [23].

4. COPD as a Disorder of Distal Airway Homeostasis, Life-Course Susceptibility, and Maladaptive Repair

COPD is a major global cause of both morbidity and mortality, and it is expected that its burden will remain substantial over coming decades [24], [25]. It is no more recognized as single uniform syndrome associated with smoking, but rather a heterogeneous syndrome expressed at multiple levels, including the age of onset, structural phenotype (emphysema predominance versus chronic bronchitis), rate of progression (differs substantially from a patient to the other), inflammatory pattern (different cellular and molecular profiles), and therapeutic responsiveness (variable response depending on phenotype, and inflammatory pattern); subsequently, the airflow limitation may originate not only from one pathogenic sequence but rather from several biological trajectories, which is in harmony with this review stating that affected epithelium integrity, defective epithelial repair, and decline of local progenitors' potential are at the center of chronic airway disease pathogenesis [20], [26], [27], [28], [29], [30].

The game changing idea in COPD is that it is not just a decline in lung function, but it may arise from failure to reach normal maximal lung function in early lung development [26]. This central idea shifted the concept of COPD as a purely adult acquired model to a disease in which many pathogenesis factors can be implicated including: developmental reserve, early environmental exposure, and later toxic injury; these factors can explain the heterogeneity of COPD, since it is a late expression of defective early lung growth and differentiation. This does not implicate that every early life functional abnormality is a direct antecedent of COPD. The principal idea is that all the early life abnormalities and developmental disadvantages increase the susceptibility to airflow limitation which can explain why there are individuals that do not follow the classical model of accelerated adult decline alone [28], [31], [32], [33].

From an anatomical and pathological standpoint, COPD is an affection of small airway and terminal bronchiolar compartment alongside with parenchymal destruction. It has been demonstrated basically that small airway obstruction in COPD is associated with many additional lesions including airway-wall thickening, inflammatory infiltration, fibrosis, mucus accumulation, and luminal narrowing. Advanced researches stated that narrowing and loss of terminal bronchioles occur early in disease evolution, which supposes that distal conducting airway is an origin site of disease, rather than a victim of downstream injury [34], [35].

At histological level, lesions found in COPD include goblet-cell hyperplasia, mucus plugging, basal-cell hyperplasia, ciliary dysfunction, altered epithelial polarity, and barrier disruption, which reinforces the idea that all of these lesions are result of maladaptation of epithelial remodeling and restoration [20], [22], [34], [35], [36], [37].

Contribution of club cells in distal airway compartment is substantial since they contribute to xenobiotic metabolism, secretory balance, innate defense, and epithelial maintenance. However, they should not be considered as the exclusive progenitor in this airway segment, their importance in COPD physiopathology is in their sensitivity to environmental pollutants and airborne toxicants leading to altered club cell's identity, less protective epithelial properties, and less differentiated state [2], [21], [36].

The second component in abnormal repair in COPD is basal cells, as the principal progenitor population in proximal airway; basal cells can differentiate into multiple luminal lineages [2], [4], [12]. Chronic smoking appears to induce defective epithelial repair through a process of declined regeneration and abnormal differentiation. Once again, COPD epithelium is persistently misrepaired instead of being simply damaged [6], [22], [38].

Normal healthy lung produces excessive mucus as adaptive mechanism in acute situations; this mucus plays the role of trap of inhaled particles and inflammatory material and participates -in this way- efficiently in local defense; mucus is obtained through a process in which there is an increase in progenitor cells transforming into secretory cells. However, in pathologic state, mucus secretion becomes chronic, resulting in defective mucociliary clearance which promotes luminal stasis and subsequent obstruction that creates a suitable environment for microbial persistence which strengthens inflammatory pathways. This is another proof showing that physiological adaptive mechanisms of epithelial airways could lead to remodeling abnormalities under sustained stress conditions [20], [30], [35], [37].

Taken together, new evidences support the idea of considering COPD as a homeostasis disorder shaped by the contribution of chronic environmental injury, regional progenitor vulnerability, and maladaptive epithelial repair. Traditional treatment of COPD relies basically on bronchodilators and anti-inflammatory agents which can be considered as symptomatic treatment from this standpoint, this implicates a comprehensive new approach that aims restoring barrier and mucociliary function, normalizing regenerative response, and preserving progenitors' potential [2], [20], [21], [29], [31].

5. hiPSC-Derived Airway Systems for Human Disease Modeling in Chronic Pulmonary Disease

Current researches in chronic airway diseases rely generally on animal models in preclinical systems for human physiopathology and therapeutic response despite their limitations especially in respiratory field, since airway epithelium has several regional specialization differences between human and animal models which makes them non effectively representative [30], [39]. hiPSC-derived airway systems place epithelial homeostasis, regional progenitor biology, and regenerative strategy within a manipulable human experimental framework. Accordingly, hiPSC platforms are useful not only for modeling differentiated epithelial phenotypes, but also for reconstructing key stages of human respiratory lineage specification that are otherwise difficult to access experimentally. This makes hiPSCs ideal for chronic airway disorders that have life-course determinants, including COPD [32], [33], [40].

hiPSCs allow guided differentiation after reprogramming, which avoids using embryonic pluripotent cells, in this way a progressive interrogation could be performed concerning developmental programs relevant to airway specification and epithelial vulnerability [41], [42].

hiPSCs production is similar to developmental logic. First, somatic cells are reprogrammed into pluripotent cells; then, these cells are guided through multiple stages including: definitive endoderm and anterior endoderm, then toward NKX2.1-positive respiratory progenitors, to get finally proximal airway epithelial lineage. Foundational studies established the possibility of three-dimensional lung model from hiPSCs, as well as functional epithelium with its region-specific progenitors which have the potential of auto-renewal and differentiation, this system has all structural and functional characterizations of normal airway epithelium such as polarity, secretion, barrier formation, with ciliary activity [7], [9]. These properties can be also recreated for every feature of chronic disease providing an identical disease-like renewable human epithelium possessing the same properties that can be interrogated under controlled conditions.

Ahmed et al, provided an example for generating a COPD-like airway epithelium by generating as a first step hiPSCs from airway epithelium of patients having severe COPD, then directing differentiation to airway epithelium in air-liquid interface which cannot be distinguished from control donors. This system is mechanistically more informative because it allows an accurate exploration of epithelial instability and provides a platform on which we can test regenerative and adaptive strategies in human tissue context, which is not possible on full mature COPD tissue [8], [41], [43].

Despite all these advantages hiPSC airway systems do not reproduce all multicellular complexities and interactions of human COPD, this includes long duration smoke exposure, stromal remodeling, immune-epithelial response, extracellular matrix alteration, vascular change, microbial interactions, and aging-associated states. In this manner hiPSC airway models are considered as mechanistic and preclinical tools that can reduce the gap between descriptive pathology and experimentally testable human epithelial biology [2], [44].

6. hiPSC-Derived Airway Systems for Emerging Epithelial Reconstruction in Chronic Pulmonary Disease: limitations and perspective

The use of hiPSC derived airway systems in cystic fibrosis has already proven its efficiency, in this case hiPSCs belonging to patients have been used to test new drugs and perform gene correction studies. But as stated in the last chapter, hiPSCs in COPD should be considered as mechanistic and preclinical tools, since it is a complex acquired disorder [10], [11], [41].

The ultimate treatment in advanced respiratory deterioration in COPD is lung transplantation. Nevertheless, it is neither an easy technic, nor a definitive solution: lungs donors are rare; after transplantation, a lifelong aggressive immunosuppression is essential; and complications are multiple including chronic lung allograft dysfunction, infection, and malignancy. Besides, lung transplantation in COPD replaces the failing organ, but does not repair underlying epithelial abnormalities seen previously [45], [46], [47]. For that reason, epithelial reconstruction from hiPSC derived airway cells should be a track to follow, despite still not being a real alternative to lung transplantation.

hiPSCs are in continuous development toward clinical translation, with more than one hundred regulatory approved clinical trials worldwide; however, in the lung, the strongest proof-of-concept is preclinical, in fact Ma et al, showed that primary or pluripotent stem cell-derived airway basal cells can engraft the injured airway epithelial stem-cell compartment, generate stable multilineage airway epithelium, and sustain long-term serial reconstitution in vivo [48],[49]. This study represents a major conceptual advance because it directly links airway progenitors' biology to functional epithelial reconstruction, although substantial challenges related to manufacturing, product standardization, delivery, niche access, durability, and safety remain unresolved [48], [50].

7. Conclusion

Contemporary evidences consider chronic airway diseases as disorders of epithelial stability and repair failure, rather than a purely inflammatory condition. COPD is an affection of distal airway compartment in which epithelial injury, lineage imbalance, impaired progenitors' function, and defective restoration of epithelial integrity are the main mechanisms.

Regeneration of a whole airway epithelium similar in all its structural and functional aspects is already a fact. hiPSCs-derived airway systems have proven their superiority in COPD modeling comparing to animal models and full mature COPD tissue, this superiority comes from the possibility of providing a renewable genetically defined epithelium, possessing all capabilities to be interrogated under controlled conditions, despite being a reductionist approach considering COPD and lung complexity.

Translational potential of hiPSCs-derived airway epithelium seems to be promising according to new proof-of-concept studies, especially if we take in consideration lung transplantation restraints in end-stage COPD. However, hiPSC-based airway reconstruction should presently be regarded as an emerging regenerative platform rather than a clinical alternative.

Compliance with ethical standards

Disclosure of conflict of interest

Author does not have financial or non-financial interests to disclose.

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