# Shared epithelial pathways to lung repair and disease

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ABSTRACT Chronic lung diseases present tremendous health burdens and share a common pathobiology of dysfunctional epithelial repair. Lung adenocarcinoma, the leading cancer killer worldwide, is caused mainly by chemical carcinogens of tobacco smoke that induce mutations in pulmonary epithelial cells leading to uncontrolled epithelial proliferation. Lung epithelial cells that possess the capacity for self-renewal and regeneration of other lung cell types are believed to underlie the pathobiology of chronic obstructive, fibrotic and neoplastic lung disorders. However, the understanding of lung epithelial progenitor cell hierarchy and turnover is incomplete and a comprehensive model of the cellular and transcriptional events that underlie lung regeneration and carcinogenesis is missing. The mapping of these processes is extremely important, since their modulation would potentially allow effective cure and/or prevention of chronic lung diseases. In this review we describe current knowledge on cellular and molecular pathways at play during lung repair and carcinogenesis and summarise the critical lung cell populations with regenerative and cancerous potential.

## Introduction

Lung cancer, chronic obstructive pulmonary disease (COPD) and lower respiratory infections causing septic and fibrotic sequelae were among the top five leading causes of death in the 2010 Global Burden of Disease study [1], claiming altogether >7 million lives in that year. The epidemic of lung cancer appears to be on a continuous rise, despite smoking prevention and cessation programmes, as evident from its global death toll in 2012 and the comparative 2005–2015 trends in the Global Burden of Disease cancer network study [2, 3]. Human lung cancers are typed into two main histopathological groupings which, in addition, reflect treatment response and prognosis: small cell lung cancer and nonsmall cell lung cancer (NSCLC). NSCLC, including mainly adenocarcinoma and squamous cell carcinoma, accounts for ~80–85% of lung cancer cases, and adenocarcinoma, its main subtype, increasingly affects current, ex- and even

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never-smokers [4–6]. Chronic lung diseases, such as COPD and idiopathic pulmonary fibrosis (IPF) are generally accepted to arise from chronic epithelial injury and incomplete or aberrant repair processes [7–11]. In contrast, lung cancer is caused by tobacco chemical-induced mutations in pulmonary epithelial cells, leading to uncontrolled cellular proliferation [12–14]. Despite significant efforts, it is still unclear whether the primary lesions of chronic obstructive, fibrotic and neoplastic disorders occur in the airways, the alveoli or both epithelial compartments, while cells with repair potential occur in large and small airways, as well as alveoli [15–20]. Although the alveoli execute the main function of the lungs, *i.e.* gas exchange, multiple lines of evidence indicate that the primary pathogenic abnormalities of chronic obstructive, fibrotic and neoplastic disorders can also occur in the airways, in addition to the alveoli [10, 11, 21, 22]. In addition, lineage-specific genes encoding epithelial proteins that support the physiological functions of the lungs were recently shown to suffer noncoding insertions and deletions in lung adenocarcinoma, lending further support to the longstanding notion that epithelial cells that express lung-restricted proteins are the cellular sources of lung cancer [23]. Collectively, the available evidence indicates that the same lung epithelial cells that maintain the lungs in adulthood and are responsible for their repair after injury are the culprits in chronic lung diseases and cancer.

## Lung cells with regenerative potential

The identification of lung cellular populations with repair and renewal capacities has been an area of intense investigation and has yielded several candidate stem/progenitor cell lineages confined to spatially distinct compartments of the pulmonary epithelium that express discrete markers. Notably, most of our knowledge on the cellular hierarchy of the lung epithelium and the relative contributions of each epithelial cell lineage to lung homeostasis after injury stems from studies on mouse models. In the mouse, airway stem cell niches have been identified in tracheal submucosal gland ducts, neuroendocrine bodies (NEB) and the broncholalveolar duct junction (BADJ), the region where the airways transition into alveoli [24–29]. The epithelium of the large airways consists of ciliated cells effecting mucociliary clearance and expressing acetylated tubulin 1A1 and the transcription factor FOXJ1, club cells secreting thin mucus and expressing club cell secretory protein (also known as club cell 10-kDa protein, encoded by secreted uteroglobin 1a1 (*Scgb1a1*)), goblet cells secreting thick (viscous) mucus and expressing mucins 5A–5C, neuroendocrine cells organised in NEBs expressing neural differentiation markers and basal cells expressing transformation-related protein-63 and cytokeratins-5 and/or -14. The epithelium of smaller airways contains club, ciliated and neuroendocrine cells, while the BADJ consists mainly of club cells and cells with dual club/alveolar type II (ATII) properties called bronchoalveolar stem cells (BASCs) [19]. The alveolar epithelium is composed of alveolar type (ATI) cells adapted for optimal gas exchange and ATII cells, the main producers of surfactant proteins A–D and the stem cells of the distal lung [16, 23, 24]. Proximal airways as well as the distal bronchioles of the human lung are lined by a pseudostratified epithelium containing basal, secretory (club and goblet), ciliated and neuroendocrine cells, while human alveoli, like those in mouse lungs, are comprised of ATI and ATII cells [30–32]. For obvious reasons, not many studies investigating human lung stem cells exist. However, accumulating evidence suggests that basal cells could represent a multipotent population of stem cells, sustaining human lung homeostasis and probably contributing to disease susceptibility [31, 33]. Furthermore, an important role for ATII cells in human alveolar maintenance and repair has been proposed [15].

## Cellular pathways to lung repair, disease and cancer

The lungs constitute the body's largest interface with the external environment. The ~90 $m^2$ of alveolar surface area of a resting adult come in contact with and filter >10 $m^3$ of ambient air on a daily basis to sustain gas exchange. Hence, stochastic and repetitive environmental noxious stimuli including tobacco-contained and other chemicals, bacterial or viral pathogens, inhaled particles, home pneumotoxins, *etc.* continuously insult the lungs, even during unchallenged ageing. In addition to this background of everyday hits, the lungs sustain massive insults that ensue sporadically in cases of infection, aspiration, sepsis and other acute lung injuries. Lung stem/progenitor cells, including bronchial and alveolar epithelial cells, physiologically display sufficient repair and renewal capacity and phenotypic plasticity to maintain lung structure and function in response to chronic and acute noxious stimuli.

In the mouse lung, resting-state homeostasis is achieved mainly *via* self-renewal and concomitant generation of heterotypic lung cells from basal, club, BASC and ATII cells. It has been shown that basal cells can give rise to ciliated and club cells [26, 28]. Club cells maintain their own population and replenish ciliated cells, and as such maintain the bronchiolar epithelial structural and functional integrity [27, 28], while ATII cells are able to self-renew and give rise to ATI cells [15, 16].

How are cellular dynamics altered upon acute and more extensive lung injury? Airway epithelial regeneration has been widely studied after naphthalene injury in mice, which selectively depletes the vast majority of club cells. These studies demonstrated that damaged airways are regenerated by a small, variant

club cell population adjacent to NEBs and in the BADJs, which is resistant to naphthalene toxicity and expands post-injury to replenish the damaged airways [17, 18]. Furthermore, BASCs were shown to possess bronchial regenerative potential post-naphthalene injury [19, 34]. An exciting notion proposed by TATA *et al.* [35] is that *Scgb1a1*$^+$ cells can de-differentiate to give rise to basal cells. After lung injury, goblet cells are replenished by *Scgb1a1*$^+$ cells, but they might also derive from ciliated Foxj1$^+$ cells, albeit to a lesser extent [36, 37]. Conversely, ATII cells are considered to be the main cellular population regenerating the alveolar compartment, able to give rise to both ATI and ATII cells after alveolar damage induced by bleomycin [15], conditional expression of diphtheria toxin by alveolar cells [15] or hyperoxia [16, 27]. However, studies describe an emerging role for *Scgb1a1*$^+$ club cells in the regeneration of both ATI and ATII cells following severe bleomycin-mediated injury [29]. In line with these observations, unpublished data of the authors support that distal alveolar epithelium is enriched in *Scgb1a1*$^+$ cells after bleomycin- and hyperoxia-induced lung injury, in accordance with previous findings [38, 39], as well as during unchallenged ageing. Whether these distally located, regenerating *Scgb1a1*$^+$ cells are due to the expansion of a distal basal cell population or to the activation of airway phenotypic markers in distal alveolar stem cells or to an actual migration of bronchial epithelial cells from the proximal airways remains to be investigated.

In chronic obstructive, fibrotic and neoplastic lung disorders, the normal balance of pulmonary cell death (injury) and life (repair) is tilted towards disease, manifested by the insufficiency of the lungs to perform gas exchange. The greatest evidence that chronic obstructive, fibrotic and neoplastic lung disorders are the result of abnormal epithelial homeostasis in response to chronic and acute environmental stress is their association with age [40] and smoking (figure 1). Interestingly, evidence suggests the implication of airway cells in human alveolar diseases. Indicatively, the pathogenesis of IPF has been associated with deregulated expression of MUC5B, a marker of goblet airway epithelial cells [22]. In patients with IPF, it has been suggested that regeneration of the fibrotic lung may be partly mediated by distal bronchial club or basal cells [9]. Furthermore, there is evidence that the emphysematous destruction in COPD is associated with narrowing and loss of terminal bronchioles [11].

The identification of lung cellular populations with stem cell characteristics has provided a valuable tool in the dissection of the underlying mechanisms of lung carcinogenesis, since stemness and oncogenic signalling in lung adenocarcinoma-initiating cells were shown to collide and to be druggable [41]. As the leading cancer killer worldwide, lung adenocarcinoma is caused mainly by chemical carcinogens in tobacco smoke that induce mutations in multiple genes of various distal pulmonary cells [12, 13], several pulmonary lineage tracing studies utilising targeted expression of oncogenes in the respiratory epithelium have been performed. However, despite considerable efforts, no definitive answer exists yet, as these studies incriminated different cells as progenitors of lung adenocarcinoma in adult mice: airway epithelial cells including basal and club cells, ATII cells and/or BASCs with dual ATII/club properties [16, 19, 20, 42–45]. In fact, new insights suggest that the molecular signature, like *KRAS* mutation or Sox2, Notch and Lkb1 signalling, is a crucial factor determining the cellular origin of cancer [46–48]. Similar studies on mouse

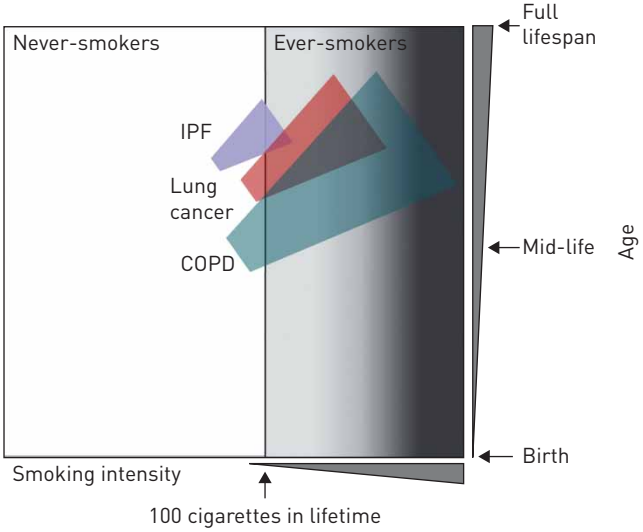


FIGURE 1 Schematic illustration of approximate overlap of smoking with chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF) and lung cancer, drawn based on data from [1–3, 7, 8, 40].

models of lung squamous cell carcinoma have validated the oncogenes identified by human sequencing studies as causative of the disease, but have not yet unequivocally identified the cellular basis of the disease, even though basal cells are an attractive candidate [24, 49].

Importantly, recent studies suggest that the mutational landscape of human lung adenocarcinoma is closely mirrored by tobacco carcinogen-induced murine lung tumours, and not by lung cancers triggered by transgenic expression of oncogenic *KRAS*$^{G12C}$ or *KRAS*$^{G12D}$ mutations in the respiratory epithelium [14]. To this end, we have used chemical carcinogens contained in tobacco smoke in order to inflict lung adenocarcinoma in mice, in conjunction with accurate mouse models of continuous respiratory epithelial cell marking. Our unpublished results support an important role for the airway transcriptional signature in the development of lung adenocarcinoma, as we detected both airway and alveolar gene expression signatures in tobacco chemical-induced lung adenocarcinomas of mice.

## Molecular signalling events in the injured and precancerous lung

Lung adenocarcinoma and squamous cell carcinoma have been associated with mutations, overexpression or loss of function of specific genes in distinct molecular pathways [13, 24, 25]. For example, indicative genes involved in squamous cell carcinoma include sex-determining region Y-box 2 (*SOX2)*, fibroblast growth factor receptor 1 (*FGFR1*), phosphatase and tensin homologue (*PTEN*), cyclin-dependent kinase inhibitor 2A (*CDKN2A*), tumour protein 53 (*TP53*), and many more [50], while human adenocarcinomas have been associated with mutations in the Kirsten rat sarcoma viral oncogene homologue (*KRAS*), epidermal growth factor receptor (*EGFR*), and v-Raf murine sarcoma viral oncogene homologue B (*BRAF*) genes, *etc*. [13].

Interestingly, molecular signalling in lung cancer and chronic lung diseases often coincides, raising the possibility of a stepwise pathobiology. For example, *Wnt* pathway genes are known to be upregulated in NSCLC [51], but they are also involved in the pathogenesis of COPD [52]. Wnt signalling induces proliferation of BASCs [53] and this could represent a potential molecular link between emphysema and cancer. Along these lines, several epithelial molecular pathways with prominent roles in lung homeostasis, lung cancer and chronic lung diseases have been described. Indicatively, transforming growth factor (*TGF*)-$\beta$ signalling underlies asthma, COPD and lung cancer [54–56], hedgehog (*Hh*) signalling can interfere with lung repair and tumorigenesis [57, 58], Notch 3 expression regulates basal cell numbers and is involved in COPD and possibly in lung cancer [59, 60], while *FGF1* signalling can link IPF and lung cancer [50, 61]. Of course, additional pathways possibly linking chronic lung diseases and lung cancer include inflammatory signalling caused by tobacco smoke exposure, angiogenic signals and many more that are not in the scope of this mini-review. These signalling pathways, which are commonly involved in the pathogenesis of chronic lung diseases and lung cancer, such as the nuclear factor-κB pathway which is critically involved in both COPD and lung cancer, are lucrative potential drug targets for the simultaneous enhancement of lung regeneration and prevention of neoplasia [62, 63].

## Conclusions

It is becoming increasingly evident that resident airway and alveolar cells display dynamic changes and marked plasticity of gene expression and/or localisation that are cardinal for pulmonary regeneration and neoplasia. Disruption of this homeostatic potential underlies several lung diseases. Therefore, understanding the mechanisms of lung regenerative capacity and elucidating the transcription programmes that are activated during lung repair, disease and carcinogenesis will probably identify novel therapeutic targets.

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