# Deregulation of Slug/Snail2 and TGF-$\beta$ crosstalk in airway epithelial stem/progenitor cells: A key link between COPD and lung cancer?

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Commentary

# Deregulation of Slug/Snail2 and TGF-β crosstalk in airway epithelial stem/progenitor cells: A key link between COPD and lung cancer?

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## Abstract

This commentary focuses on two recent publications showing deregulation of the transcription factor Slug/Snail2 and TGF-β function in primary bronchial basal/progenitor cells of patients with Chronic Obstructive Pulmonary Disease (COPD) and the impact on proliferation and the expression of genes involved in stem cell maintenance. We discuss the molecular mechanisms related to the exhaustion of airway basal stem/progenitor cells in tobacco smoke-induced COPD, as well as putative links between COPD and lung cancer at the molecular level. The focus of the commentary is a potential central role of the crosstalk between Slug/Snail2 and TGF-β mechanisms, and perspectives for identification of new biomarkers and/or therapeutic targets or therapy for preventing and treating these diseases.

**Keywords:** Chronic obstructive pulmonary disease (COPD), Lung cancer, Human primary bronchial basal stem/progenitor cells, Transforming growth factor (TGF)-β, Slug/Snail2 transcription factor

## Introduction to COPD and Airway Remodeling

Chronic Obstructive Pulmonary Disease (COPD) is a respiratory disease characterized by progressive and irreversible loss of respiratory capacity. Different stages of the disease have been defined based on the decrease in respiratory capacity of the patient that can range from mild to severe. COPD results essentially from inhalation of toxic gas and particles, and a major cause is tobacco smoke. Continual exposure to the compounds in tobacco smoke induces tissue damage, leading to irreversible morphological and functional alterations in the lungs.

COPD is a complex disease and is characterized by a combination of structural and inflammatory changes. In addition to a high level of inflammation, a remodeling of the airways in the COPD patients is leading to an increase in the thickness of the airway wall and a narrowing of the airway lumen. A central issue in airway remodeling is that chronic exposure to tobacco smoke directly affects the morphology and function of the epithelium lining the airways. [1]. Whereas COPD has been initially seen as an inflammation-driven disease, and research and therapy were focused mainly on the treatment of airway inflammation, only recently airway remodeling is increasingly considered as the primary feature underlying COPD development [2,3].

This change of paradigm, from COPD being essentially an inflammatory disease to COPD being primarily an airway remodeling disease, changed the focus of the research toward better understanding of the airway remodeling and its mechanisms with a particular emphasis on the impact of tobacco smoke on the occurrence of the epithelial abnormalities and their link with COPD initiation and development [3]. The work that we have recently published [4,5] is part of this area of research and stems from several recent advances in understanding the causes of airway epithelium deregulations in COPD smokers.

## Background/State of the Art on COPD and Airway Epithelial Abnormalities

### Basal stem/progenitor cell reprogramming

A mix of basal, ciliated, and mucus-producing goblet cells essentially composes the pseudostratified

airway epithelium. Basal cells contain the adult stem/progenitor cells of the airway epithelium that can either self-renew and/or differentiate in ciliated or goblet cells to repair the epithelium after injury [6].

The abnormalities in the COPD airway epithelium consist mainly of areas of squamous metaplasia and goblet cell hyperplasia at the epithelial luminal side and, at the basal membrane, of wall fibrosis and thickening [7,8]. Recently, it has been reported that basal stem/progenitor cell number is reduced in COPD and that they regenerate an epithelium with a reduced number of ciliated cells and relatively more basal and goblet cells. Several studies provide evidence that tobacco smoke has a major impact on basal stem/progenitor cells causing aberrant repair processes and abnormalities in airway epithelium of COPD. This would be the result of a deregulation of their genetic program leading to an imbalance in their fate and a pathological differentiation process. [6,9-11]

Aberrant expression of epigenetic markers and methylation modifications have been linked to COPD, suggesting that epigenetic modifications are involved in this reprogramming [12-14].

**Field of injury implicating large and small airways**

The loss of respiratory capacity characterizing COPD has been linked to small airways. A correlation between disease severity and the degree of small airway remodeling, in particular epithelial anomalies, has been shown [15,16]. However, several studies have also revealed that basal stem/progenitor cells exposed to tobacco smoke keep the memory of the exposure, likely through epigenetic modifications, and that a "field of injury" is established all along the airway epithelium with both small and large airway epithelia presenting lesions. In addition, previous studies imply that basal progenitors from large airways reflect the dysfunction of progenitors of the small airways and that molecular changes in large airways are also seen in small airways. This makes cells from large airways a good model to study the molecular mechanisms leading to epithelial abnormalities and their link with COPD pathogenesis [10,11]

**TGF-β signaling and epithelial-mesenchymal transition at the crossroad of COPD and lung cancer**

Studies have shown that mature epithelium from COPD airways present features of Epithelial-Mesenchymal Transition (EMT), including myofibroblast formation. Research that followed has investigated the possibility that EMT is active and pathogenic in the airways of smokers with COPD. The data obtained suggest that EMT plays a major role in COPD as an airway remodeling disease and this led to the hypothesis that COPD may be an EMT driven process [17,18].

COPD smokers have an increased risk of lung cancer compared to non-COPD smokers, in particular of squamous carcinoma in the proximal bronchus [19,20]. Deregulation of the COPD airway epithelium is likely involved in this association and it has also increasingly been linked with EMT. In a recent study, EMT activity in non-small cell lung cancers has been directly related to EMT in non-cancerous airways of the same patients [21].

Transforming Growth Factor (TGF)-β is known to be, in certain conditions, an EMT-inducing factor [22,23]. It is found at high levels in COPD lung tissues and clinicopathologic studies have shown that TGF-β is likely to have a major EMT-inducing role in COPD [24,25]. TGF-β is particularly interesting as its function is complex and it has a wide spectrum of effects, which can be antagonistic depending on the cell state. It has been shown to play a role in the fate of stem/progenitor cells. Whereas it is a cell cycle inhibitor in normal cells, it can act as a tumor promoter in malignant cells [26-28].

## Aims and Main Findings

**Experimental approach: Design and hypothesis**

Our aim was to further understand the reprogramming of basal stem/progenitor cells in COPD, and to search for molecular links between COPD and lung cancer. For this, we first wanted to identify and compare the genes that are involved in the genetic differentiation program of normal and COPD basal stem/progenitor cells. To identify key genes involved in the regulation of basal stem/progenitor cell fate and differentiation process, we choose to identify the genes involved at the onset of differentiation rather than genes involved in the mature cell functions.

As an experimental model we used primary bronchial epithelial progenitors cells cultured in the Air-liquid Interface (ALI) system. Bronchial progenitor cells, which originate from large airways, are easier to obtain and their molecular dysfunctions reflect to some extend that of progenitors of the small airways [10,11]. Primary bronchial epithelial progenitors cultured at the ALI are able to reconstitute the pseudostratified bronchial epithelium. Importantly, they retain the memory of the tissue of origin and when isolated from COPD patients, they reconstitute an epithelium with abnormalities characteristic of COPD [18,29,30].

Since we anticipated that many genes would be involved in the onset of differentiation, we choose to particularly focus on genes downstream of the transcription factor Slug/Snail2. Like other members of the Snail family of EMT-inducing transcription factors, Slug/Snail2 is overexpressed and involved in EMT-related processes in several cancers, including lung. [31]. In contrast to other EMT-inducing transcription factors, Slug/Snail2 is expressed in adult stem/progenitor cells in normal airway epitheliums. It was found enriched in both mouse and human airway basal cells and expressed in spheroids of stem/progenitor cells isolated from human adult airway epithelia [32-34]. Moreover, TGF-β, that is at high levels in COPD lung tissues and involved in EMT, is also known to regulate the expression of Slug/Snail2 [24,25,35]. We then hypothesized that Slug/Snail2, in combination with TGF-β, could be a key transcription regulator involved in adult airway basal stem/progenitor cell fate, and that the deregulation of this crosstalk could lead to the airway epithelial dysfunction observed in COPD.

**Data generated and main results**

We have generated two datasets from our experiments. One corresponds to expression data from primary human bronchial epithelial basal cells from non-COPD and COPD smokers that had Slug/Snail2 knocked down and the other to expression data from primary human bronchial epithelial basal cells from smokers non-COPD and COPD in ALI culture at the onset of differentiation in absence or presence of TGF-β.

By combining these two datasets, we have selected the genes that are repressed downstream of Slug/Snail2 and that respond to both differentiation and TGF-β. These genes, either from normal or from

COPD cells, were classified in 4 groups according to their response to differentiation and TGF-β (Figure 3a in [4]; Figure 1a in [5]). This allowed us to visualize important differences between normal and COPD cells in the genes repressed downstream of Slug/Snail2.

In normal cells, we identified a large group of proliferation genes that are downregulated with differentiation and repressed by TGF-β, and that are not downstream of Slug/Snail2 in COPD. In COPD cells, we identified a small set of genes coding for transcription factors involved in stem cell maintenance that are downregulated with differentiation and repressed by TGF-β, and that are not downstream of Slug/Snail2 in normal cells. The study of the levels of expression of both proliferation and stem cell maintenance genes revealed that they differ between normal and COPD basal stem/progenitor cells only in presence of TGF-β. At the onset of differentiation, proliferation genes are less expressed in normal cells due in part to a higher repressive effect of TGF-β in these cells than in COPD cells. Instead, stem cell maintenance genes are less expressed in COPD cells as they are repressed by TGF-β in these cells and not in normal cells (Figure 1). In addition, we found a positive correlation between Slug/Snail2 expression levels and the repressive effect of TGF-β on the proliferation genes in normal cells only, as well as on the stem cell maintenance genes in COPD cells only.

## Perspectives for New Directions of Research

Our results reveal that the genes downstream of Slug/Snail2, which represent a mix of direct and indirect targets of this transcription factor, are deregulated in COPD basal stem/progenitor cells. In these cells, we found that, at the onset of differentiation and in presence of TGF-β, the genes involved in proliferation, independently of Slug/Snail2 pathway, are expressed at higher levels, while stem cell maintenance genes, downstream of Slug/Snail2 pathway, have their expression inhibited. We have also found that the response of COPD basal stem/progenitor cells to TGF-β differs with in particular an increase of expression of β-Catenin, which is part of a non-canonical TGF-β signaling. In addition, we showed an increase of Slug protein levels in COPD cells in presence of TGF-β, but that it was not associated with a decrease of the EMT marker E-cadherin. No difference between normal and COPD cells for the expression of EMT markers was found in undifferentiated cells and at the onset of differentiation in presence or absence of TGF-β.

At this stage of the study, our findings are mainly correlative and hypothesis generating. They will provide a base for new directions of COPD research.

**Molecular mechanisms involved in exhaustion of basal stem/progenitor cells in COPD**

The identification of genes involved in stem cell maintenance genes that are repressed by TGF-β in COPD basal stem/progenitor cells brings a new insight in the molecular mechanisms of the disease. They could be directly involved in the decrease of self-renewal and differentiation capacity of basal stem/progenitor cells and/or epithelium abnormalities observed in the airway epithelium of COPD patients [11,12]. Since these genes all code for transcription factors, they are likely among the key regulators of basal stem/progenitor cells. Their specific function and implication in the exhaustion of COPD basal stem/progenitor cells need to be further studied.

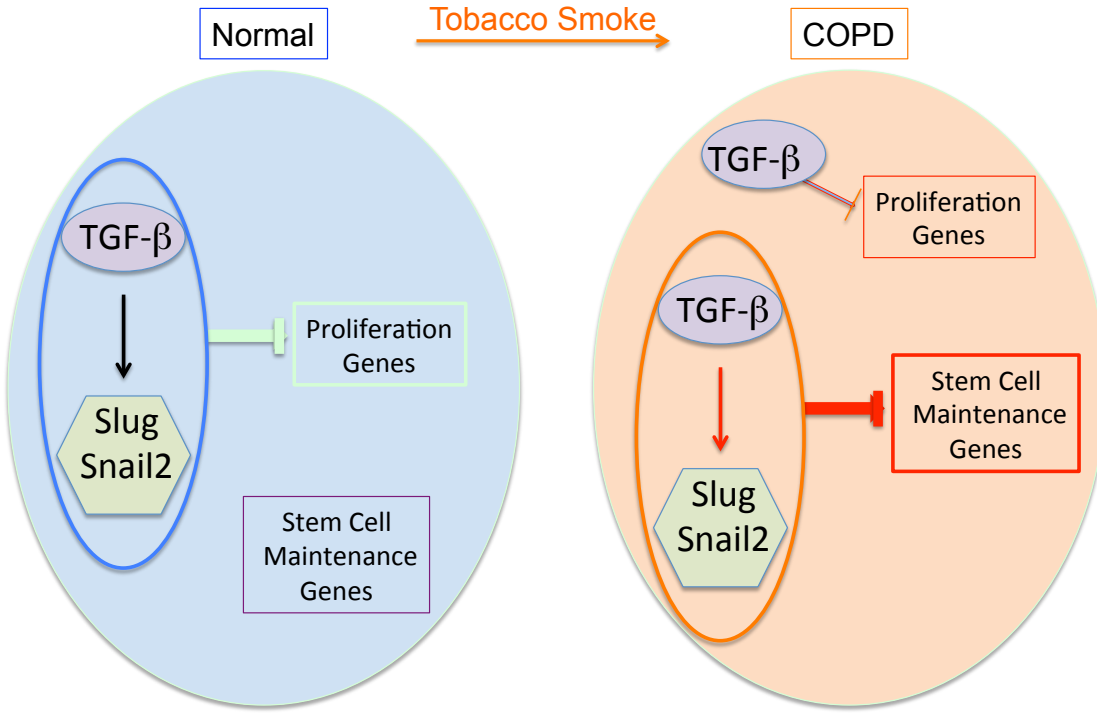


**Figure 1:** Repression of proliferation and stem cell maintenance genes by TGF-β and Slug/Snail2 in normal and COPD airway basal stem/progenitor cells at the onset of differentiation.

Our data also suggest that a crosstalk between Slug/Snail2 and TGF-β is important to further understanding the etiopathology of COPD, Slug/Snail2 may act as a mediator of TGF-β in the regulation of basal stem/progenitor cells, as it has been shown in other cells [36,37]. However, further experiments are required to confirm this.

**Slug/Snail2 and TGF-β signaling as molecular links between COPD and lung cancer**

The implication of Slug/Snail2 and TGF-β in the regulatory changes suggests that this is a good starting point to identify molecular mechanisms involved in the association between COPD and lung cancer. The finding that Slug/Snail2 in combination with TGF-β is involved in the repression of proliferation genes at the onset of differentiation in normal basal stem/progenitor cells and that this repression is deregulated in COPD cells seems particularly interesting for the search of the molecular links between COPD and lung cancer.

TGF-β function is complex with a wide spectrum of effects. It can have antagonistic effects depending on cell state: it can act as a cell cycle inhibitor in normal cells and a tumor promoter in malignant cells [26,27]. We speculate that the difference between normal and COPD cells that we found could reflect such antagonistic effects, with COPD cells being in a premalignant state and imprinted with epigenetic modifications that make them permissive for oncogenic mutations to initiate lung cancer. The change in Slug/Snail2 downstream genes could reflect difference in TGF-β signaling between normal and premalignant cells. Further studies in that direction could lead to understand at least part of the association of COPD and lung cancer.

It is also important to note that in COPD cells we did not observe a decrease of the EMT marker E-cadherin, even when treated with TGF-β. Other EMT-inducing transcription factors had a similarly low expression in both normal and COPD cells, suggesting that Slug/Snail2 is not an EMT-inducer in undifferentiated basal stem/progenitor cells or at the onset of their differentiation. However, we speculate that the deregulations observed in the basal stem/progenitor cells in COPD could ultimately lead to a shift in Slug/Snail2 function, which then starts acting as an EMT-inducing factor. It has been reported that Slug levels of expression define its function and overexpression of Slug induces EMT in epithelial cells [38,39]. Slug protein is at higher levels in COPD cells in the presence of TGF-β. The high levels of TGF-β found in the lungs of COPD patients increase with the progression of the disease and could increase during repeated injury. This could explain the higher EMT features found in mature COPD epithelium and the increased risk for COPD patients to develop lung cancer.

More studies are required to better understand the central role of TGF-β and its link with Slug/Snail2 transcription factor in the deregulation of airway basal stem/progenitor cells. However, all our findings point to a key role of these deregulations in the transition from normal to COPD cells induced by tobacco smoke. In addition, both TGF-β and Slug/Snail2 have been shown to be involved in lung cancer, making them good candidates to better understand both the molecular mechanism involved in the exhaustion of basal stem/progenitor cells in COPD and the molecular link between COPD and Lung cancer. Such studies could open up new directions to identify new markers or therapeutic targets or therapy for preventing and treating these diseases.

## Conflict of Interest

The author declares no conflict of interest.

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