



Commentary

WNT/ β -catenin pathway: A novel therapeutic target for attenuating airway remodelling and EMT in COPD

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COPD is a fatal chronic lung disease with increasing global prevalence, soon estimated to be the third leading cause of death worldwide. Cigarette smoking is attributed as the primary source that afflicts the lungs in the first world nations; however, increasing environmental, indoor, and outdoor pollutions could further influence disease outcomes. Significant pathological changes in COPD, include irregular inflammatory pattern, airway and parenchymal remodelling, ultimately small airway fibrosis and obliteration, it is also associated with huge risk for lung cancer [1].

The epithelial lining of the lung forms the outer protective barrier against environmental toxins that emanate from smoke and microbial infections. The fundamental alterations that occur in epithelial cells involve pathways associated with both epigenomic and transcriptomic reprogramming. This altered dynamic response provides credence to processes such as epithelial to mesenchymal transition (EMT), wherein transitional changes fundamentally occur due to epithelial cell plasticity, with basal epithelial cells most vulnerable to such transformation [2]. In an EMT environment, epithelial cells progressively lose their polarity and adhesiveness and become migratory by gaining mesenchymal characteristics. Several pathways are demonstrated to actively promote EMT in COPD and other fibrotic lung diseases such as interstitial pulmonary fibrosis [3]. Major players that promote EMT include TGF- β , WNT, Notch, Twist, Snail and Sonic Hedgehog signalling [3]. Although WNT/ β -catenin pathways are identified to play a crucial role in early human lung morphogenesis, only few studies demonstrate their dysregulation in adult tissue homeostasis, especially in airway diseases such as COPD [4].

It is thus of interest that in the recent issue of EBioMedicine, Carlier and colleagues [5] using latest cutting edge technology such as laser microdissection and RNA sequencing of large airway epithelial areas showed significant upregulation of genes and proteins associated with

the WNT/ β -catenin signalling pathway. The study portrays the intriguing role of WNT/ β -catenin relation to cellular dysfunctionality and its fundamental role in driving COPD pathology. More fascinating were the critical differences detected between the *in-situ* tissue proteins expression and those from the mechanistic *in vitro* airway liquid interface (ALI) study outcomes. The key difference was observed with increases in epithelial mucin protein expression which positively related to β -catenin levels in proximal airway tissues, though in ALI culture, a more contrasting reduction in goblet cells were found on WNT induction. Previous findings in patients with COPD have shown increase in goblet cells and mucin hypersecretion, which forms part of the chronic exacerbatory response to eliminate foreign particles and infections, especially in severe patients. Recent evidence also points to several pathways including EGFR and notch signalling to be crucial in goblet cell formation, differentiation, and secretion, which likely suggests that non-canonical induction of β -catenin could be responsible for such developments [6]. Another key finding in this study was the role of WNT in epithelial cilia formation. Extrinsic addition of WNT suppressed genes associated with cilia formation. Cilia dysfunctionality is common in smokers and patients with COPD, who tend to have shorter cilia in both large and small airways in comparison to non-smokers [6]. Although contrasting effects were observed in the *in vitro* gene regulation by WNT pathway, vis-à-vis cilia and goblet cell formation and regulation, these findings are indeed novel and provide new avenues for the future molecular understanding of WNT/ β -catenin signalling in airway remodelling.

The other vital find by Carlier et al. was the downregulation of genes associated with the epithelial junctional protein and increased epithelial polarity. Importantly an existent cross talk was observed between WNT/ β -catenin and TGF β pathways which on activation, showed an increase in activated pSMAD2 and vimentin, both critically important proteins in EMT. Other potential pathway crosstalk in EMT includes TGF β 1 and p38 MAPK/PI3K/Akt signalling pathways. They have been observed to complement each other through activation of SMAD2/3 in animal models of COPD and lung cancer [1]. However, it is essential to identify if these pathways are triggered simultaneously or feed into one another to promote the final transformation of the cells. Whatever the scenarios may be, the final outcome is the increase in nuclear translocation of β -catenin and pSMAD2/3 leading to the activation of several transcription factors that alter the functional dynamics of the epithelium, interfering with their structural integrity, leading to EMT, and making them vulnerable to disastrous outcomes [4].

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EMT is broadly categorised into three types, Type-1 occurs during embryogenesis, Type-2 in adult stage organ fibrosis, and Type-3 in epithelial malignancy [3]. We have previously shown that Type-2 EMT is active in small airways in patients with COPD leading to small airway fibrosis and Type-3 is associated with increased angiogenesis of the reticular basement membrane (Rbm), promoting squamous cells carcinomas, phenotypic signatures especially in proximal airways [4, 7-10]. As we previously reported in several of our studies, EMT in COPD is characterised by increase in mesenchymal markers in the epithelium, such as S100A4, vimentin and N-Cadherin, with associated proteolytic fragmentation of the Rbm, facilitating mesenchymal cell migration into the underlying lamina propria [3, 4, 7-9]. This Rbm disruption is driven by matrix metalloproteases [7], produced by transitioning cells, as also observed in the current study. Finally, the migrated cells transform themselves into the more active form of myofibroblasts, causing drastic changes to the overall underlying mucosa making them thickened through the accumulation of extracellular matrix proteins especially collagen and fibronectin. Mitigation strategies with inhaled corticosteroid (ICS) such as fluticasone propionate have proved useful in attenuating EMT in COPD [9], but Rbm related increased angiogenesis does not respond to ICS and may require more extended treatment periods to demonstrate their effects [10].

It is now clearly established that several pathways are closely associated with the pathogenesis of COPD, making the lungs vulnerable not only to the fundamental remodelling changes but also triggering a more transformative condition such as EMT that causes irreversible fibrosis or leads to cancer. It is imperative that these pathways be targeted with more efficient therapeutic strategies to enable better disease mitigation and management.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

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