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Bronchial epithelium as a target for innovative treatments in asthma

Delphine Gras [a], Pascal Chanez [a,b,*], Isabelle Vachier [c], Aurélie Petit [c,d], Arnaud Bourdin [c,d]

[a] UMR INSERM U1067 CNRS 7333, Aix-Marseille University, Marseille, France
[b] Clinique des Bronches, Allergie et Sommeil, AP-HM-Hôpital Nord, Marseille, France
[c] Dept. of Respiratory Diseases, CHRU Montpellier, Montpellier, France
[d] INSERM U1046, University Montpellier 1 and 2, Montpellier, France

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ABSTRACT

Increasing evidence of a critical role played by the bronchial epithelium in airway homeostasis is opening new therapeutic avenues. Its unique situation at the interface with the environment suggests that the subtle regulation orchestrated by the epithelium between tolerance and specific immune response might be impaired in asthma.

Airway mucus is acting as a physical and a biological fluid between the environment and the epithelium, synergistically moved by the cilia. In asthma, excessive mucus production is a hallmark of airway remodeling. Since many years we tried to therapeutically target mucus hypersecretion, but actually this option is still not achieved. The present review discusses the dynamic processes regulating airway mucus production.

Airway inflammation is central in current asthma management. Understanding of how the airway epithelium influences the TH2 paradigm in response to deleterious agents is improving.

The multiple receptors expressed by the airway epithelium are the transducers of the biological signals induced by various invasive agents to develop the most adapted response. Airway remodeling is observed in severe chronic airway diseases and may result from ongoing disturbance of signal transduction and epithelial renewal. Chronic airway diseases such as asthma will require assessment of these epithelial abnormalities to identify phenotypic characteristics associated with predicting a clinical benefit for epithelial-directed therapies.

Contents

Abbreviations: Ach, Acetylcholine; AHR, Airway hyperresponsiveness; ASM, Airway smooth muscle; BAL, Bronchoalveolar lavage; BEC, Bronchial epithelial cell; CF, Cystic fibrosis; CFTR, Cystic fibrosis transmembrane conductance regulator; CHI3L1, chitinase 3 like protein 1; COPD, Chronic obstructive pulmonary disease; COX, cyclooxygenase; CSE, cigarette smoke extract; DC, Dendritic cell; DHA, Docosahexaenoic acid; DLL-1, Delta like protein 1; EGF, Epithelial growth factor; EGFR, Epithelial growth factor receptor; EMTU, Epithelial–mesenchymal trophic unit; ERK, Extracellular signal-regulated kinase; ET, Endothelin; GCs, Glucocorticoids; GPCR, G protein coupled receptor; GR, Glucocorticoid receptor; HB-EGF, Heparin binding-EGF; ICS, Inhaled Corticosteroid; IgA, Immunoglobulin A; IgE, Immunoglobulin E; IL, Interleukin; IL-R, interleukin receptor; LABA, Long acting β2-agonist; LAMA, long acting muscarinic receptor; LO, Lipoxygenase; LPS, Lipopolysaccharide; LTRA, Leukotrien agonist; LXs, Lipoxins; miR, microRNA; MMP, matrix metalloproteinase; MUC, mucin; NF-kB, Nuclear Factor-KappaB; Nkx2.1, NK2 homeobox 1; NO, nitric oxide; OVA, ovalbumin; PGE2, Prostaglandin E2; pIgR, polymeric immunoglobulin receptor; PKC, phosphokinase C; PM, Particulate matter; SABA, Short acting β2-agonist; SP, surfactant protein; SPDEF, SAM pointed domain-containing Ets transcription factor; STAT, Signal transducer and activator of transcription; TACE, tumor necrosis factor-alpha-converting enzyme; TGF, Transforming growth factor; TLR, Toll like receptor; TNF, Tumor necrosis factor; TSLP, Thymic stromal lymphopoietin.

* Corresponding author at: UMR INSERM U1067 CNRS 7333, Université Aix-Marseille, Clinique des Bronches, Allergie et Sommeil, AP-HM-Hôpital Nord, Chemin des Bourrely, 13015 Marseille, France. Tel.: +33 491968631; fax: +33 491968902.
E-mail address: pascal.chanez@univ-amu.fr (P. Chanez).

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1. Introduction

There is no doubt that the prevalence of chronic airway diseases is still raising now (Baiz & Annesi-Maesano, 2012). They represent an important burden for the patients, their families and the entire society. As health care providers and researchers, we are facing a major challenge, which needs to be solved rapidly. First, most of these conditions are heterogeneous and the ways they are defined are not accurate. Second, most of the currently available treatments are directed against the symptoms. While inhaled steroids have been shown to save the lives of asthma patients, there is still no treatment clearly interfering with the natural history of COPD. Third, despite vigorous research efforts and important advances in the understanding of the mechanisms, paradigms do not change quickly and animal models — essentially used to assess short-term processes fail to be translated to chronic human diseases. Last, the time it takes to translate these findings to patient care is long, because it requires expensive and difficult clinical trials, which do not fully represent real life situations (Barnes, 2011). Bronchial inflammation was the major discovery related to chronic airway diseases in the 90's using invasive and non-invasive tools. Quickly, this paradigm was effective to affirm the need for and secure the use of the anti-inflammatory properties of corticosteroids as major controllers of asthma and, to a lesser extent, in COPD (Holgate; Barnes, 2010). In COPD, the nature of the inflammation and the role of deleterious agents (i.e. exposure to cigarette smoke and fumes) are thought to explain this decreased corticoid responsiveness. Although inflammation of the airways was clear, epithelial and smooth muscle cells and all the components of the extracellular matrix gained an importance. There is increasing and solid evidence for a key role played by the bronchial epithelium tissue at the edge of environmental triggers to produce a specific response balancing subsequent repair and inflammation. Decreased cohesion and integrity of the epithelium have been shown in animal models of COPD and asthma pleading for a fragility, which may differ across diseases and stages of severity. The impaired barrier effect may facilitate the passage of deleterious agents and/or antigens — DC caption, or the efflux of mediators and the efflux of inflammatory cells in the lumen (Uller et al., 2001). Cell abnormalities and defective apoptotic cell engulfment lead to abnormal tissue turnover and permanent activation with exaggerated release of inflammatory products and growth factors (Juncadella et al., 2013). This persistent vicious circle of activation contributes to airway wall changing in the submucosa and accumulation of mucus and cell debris in the lumen (Tam et al., 2011). Those chronic epithelium changes may contribute to airflow obstruction and hyperresponsiveness. The diseased epithelium is vulnerable and easier to activate and the effect of current airway therapies (classically a combination of corticosteroids and LABA or LAMA) is largely unknown. As a matter of concern, the epithelium is also impaired in its ability to resolve inflammation (Levy et al., 2012). Considering chronic airway disorders as belonging to epithelial diseases brings major opportunities for focused therapeutical interventions aiming to restore it as a partner of the host defense and promoting a normal healing of the airway wall.

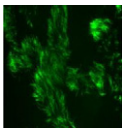
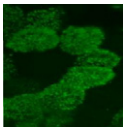
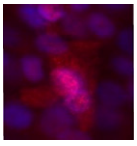
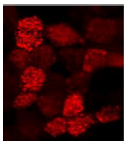
2. Dynamics of the bronchial epithelium

2.1. Structure of the bronchial epithelium

A fully differentiated epithelium is constituted of different cell types. They have first been defined by their morphological appearance. Nowadays, specific antibodies are available and used to identify cell subtypes (Table 1). Even though these reagents are not perfect (Xian & McKeon, 2012), they made it possible to describe three main cell types covering the basement membrane following a pseudo-stratified organization (Fig. 1). The alveolar structure and pathology will not be discussed here.

As it is situated at the frontier with the environment, the airway epithelium can be regarded as the perfect interface between the air and the internal milieu. Accordingly, most airway epithelial properties account for a perfect imbalance between alveolar integrity – which means a perfect filtering and removal of most air impurities on the one hand, and absence of chronic airway inflammation on the other hand – which is highly suggestive of strong immuno-modulatory abilities (Proud & Leigh, 2011). Accordingly, the airway epithelium is thought to play a decisive role when processing exogenous inhaled particles in order to elicit a highly regulated response spread from the

Table 1
Main epithelial cell types.

Cells	Picture	Antibody use	Properties	Remarks
Ciliated		Tubulin IV FoxJ1	Mucus motion. Ion transport. Cytokine production.	Specific depletion using NO_2
Goblet		MUC5AC TFF3 pIgR	Mucus production. Cytokine production.	
Basal		Cytokeratine 5/14 P63 CD151 1D9/B Trp63	Renewal and repair (proximal airway). Orientation of the epithelial phenotype. Cytokine production.	
Neuroendocrine		CGRP Chromogranin A PGP9.5		
Other club variant		CCSP, SPA, SPD CCSP, SP-C, CD34, Sca-1	Distal airway: renewal and repair. Detoxification.	Specific depletion using naphthalene