

EDITORIAL

Airway goblet cell hyperplasia in asthma: hypersecretory and anti-inflammatory?

Introduction

Increased numbers of goblet cells (goblet cell hyperplasia) is part of airway remodelling in asthma [1, 2]. The remodelling also includes epithelial proliferation, thickening of the reticular basement membrane, increased bronchial vascularity and hypertrophy of smooth muscle and submucosal glands. This 'inappropriate' remodelling is a pathophysiological process leading to clinical symptoms. For example, goblet cell hyperplasia is linked to chronic mucous hypersecretion and consequent airflow obstruction. The perceived impact of airway remodelling on morbidity and mortality in asthma has prompted the development of animal models to aid understanding of basic mechanisms underlying asthma pathophysiology and to rationalize development of therapeutic drugs [3, 4]. These models are beginning to define the pathways involved in airway remodelling. As a consequence, possible avenues to inhibition of airway remodelling, including goblet cell hyperplasia, are being delineated. However, the article by Kasper and colleagues in this issue of *Clinical and Experimental Allergy* demonstrating that hyperplastic airway goblet cells in a rat model of asthma express the anti-inflammatory and immunomodulatory molecule surfactant protein D (SP-D) [5] indicates a homeostatic mechanism to compensate for goblet cell hyperplasia (Fig. 1). This surprising observation may modify our views on pathophysiology and therapy of mucous hypersecretion in asthma.

Asthma: airway inflammation and remodelling

Asthma is a major cause of chronic illness world-wide. It can affect 5% or more of the population in industrialized countries, and is defined as a clinical entity in which airway resistance varies over short periods of time and is reversible, to a greater or lesser extent, either spontaneously or after treatment [6–8]. It is invariably an allergic condition and is characterized by airway inflammation involving Th2-lymphocytic orchestration of pulmonary eosinophilia [9, 10]. The mechanisms of the acute increases in airflow resistance, associated with breathlessness and wheezing, include contraction of smooth muscle that constricts the airways, additional luminal narrowing due to airway wall oedema, and luminal obstruction with excess mucus. In the later stages of the disease, a fixed component of airflow resistance can develop that is related to remodelling rather than just inflammation [11]. Remodelling also contributes to airway hyperresponsiveness, a feature of all stages of asthma, characterized by an exaggerated increase in airflow resistance in response to inhaled stimuli such as histamine. Thus, airway remodelling contributes to clinical symptoms in asthma. The relative

contribution to pathophysiology of each component of the remodelling process is unknown and will vary between patients. Mucous hypersecretion is one component that is currently receiving much attention.

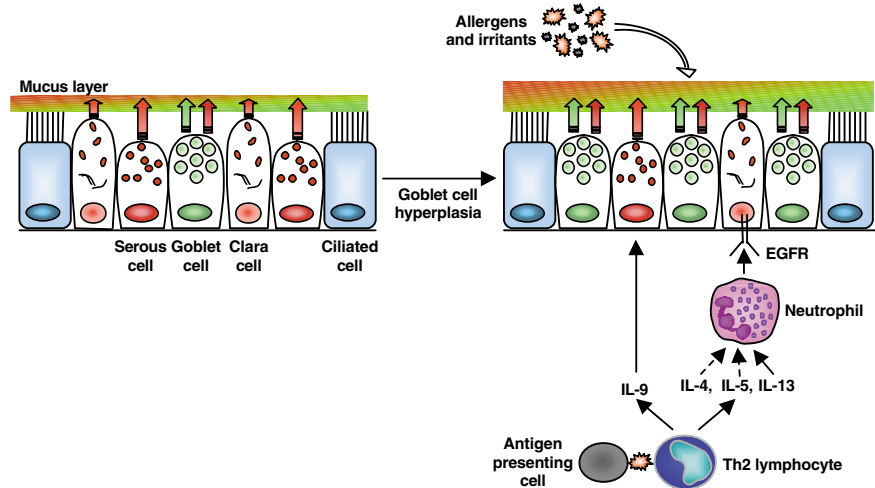
Airway mucus, mucins and secretory cells

Mucus is a complex aqueous solution of lipids and proteins that lines the airway lumen. Under normal circumstances it protects the airway epithelium from inhaled irritants. In respiratory conditions such as asthma that are associated with mucous hypersecretion, mucus ceases to be protective and, instead, contributes to pathophysiology [12]. The function of mucus is to trap inhaled particles and, by interaction with the tips of beating cilia, remove them from the airways, a process termed mucociliary clearance. Mucus requires the correct viscosity and elasticity for optimal efficiency of ciliary interaction. The viscoelasticity of the mucus is attributed primarily to its content of high molecular weight mucous glycoproteins, or mucins [13]. Mucins comprise a highly glycosylated peptide backbone (the latter termed apomucin) and are produced by surface epithelial goblet cells [14] and submucosal glands [15]. Apomucins are encoded by specific mucin (MUC) genes, with 17 human MUC genes recognized to date. Lamentably, the technology to determine which MUC gene products contribute to the formation of airway mucus lags way behind that of investigation of gene expression. Present evidence suggests that MUC5AC and MUC5B are the major gel-forming mucins in respiratory secretions from both normal subjects and patients with asthma [13]. Interestingly, although there is overlap between the two, MUC5AC appears to be predominantly a goblet cell mucin whereas MUC5B is predominantly a gland mucin [13].

Mucous hypersecretion and goblet cell hyperplasia in asthma

Airway mucous hypersecretion is a prominent feature of asthma [12, 16]. Most patients produce sputum, especially during or after an attack of asthma, and the airways of many patients dying in *status asthmaticus* are occluded by 'mucus' plugs. The increase in airway mucus is associated with an increase in the amount of mucin-secreting tissue, both goblet cells and glands. Submucosal glands are restricted to large (cartilaginous) airways from which excessive secretions, from hypertrophied glands, can be cleared by cough [17]. In contrast to glands, goblet cells line the respiratory tract down to small, non-cartilaginous airways. Cough cannot clear secretions

Fig. 1. Hypothesis for a compensatory mechanism for airway goblet cell hyperplasia. Left hand panel: normal epithelium is covered by a thin layer of mucus and comprises ciliated, goblet, serous and Clara cells. Goblet cells secrete mucins (green arrows) that contribute to formation of the mucus layer. Goblet cells, serous cells and Clara cells produce antibacterial, anti-inflammatory and immunomodulatory molecules (e.g. surfactant proteins, peroxidases and lysozyme) that contribute to airway defence (red arrows). Right hand panel: Goblet cell hyperplasia induced by airway inflammation. Inhaled allergens initiate a Th2 lymphocyte response with release of IL-4, -5, -9 and -13, each of which induce goblet cell hyperplasia either directly (e.g. IL-9) or indirectly (e.g. neutrophils and epidermal growth factor receptors (EGFR) mediate the IL-13 response). Goblet cell hyperplasia leads to mucous hypersecretion and production of a thicker mucus layer (to protect the epithelium from inhaled 'insult'). The increased number of goblet cells is at the 'expense' of serous and Clara cells. However, goblet cells also produce host defence molecules, which means that the airway inflammatory 'shield' is balanced despite loss of serous and Clara cells.



from these lower airways and mucus clearance is reliant on an intact mucociliary clearance system. Mucous hypersecretion by hyperplastic goblet cells in small airways can readily overwhelm the mucociliary escalator and lead to mucous plugging and airflow obstruction. Consequently, goblet cell hyperplasia, rather than submucosal gland hypertrophy, is perceived to have the greater pathophysiological significance for airway mucous hypersecretion.

Goblet cell numbers and volume of stored mucin are up to threefold higher in bronchial biopsies from patients with mild or moderate asthma than in controls [18]. The latter increase is associated with increased MUC5AC mucin, an observation consistent with goblet cell hyperplasia (see above). The mucin content of induced sputum was greater in moderate than in mild asthmatics, although the source of the mucin, whether salivary glands, bronchial glands or goblet cells, was unknown. Induced sputum from the controls contained half as much mucin as that from the asthmatic patients. Goblet cell hyperplasia is also a prominent feature of the airway epithelium in fatal asthma [19]. In autopsied lungs from three patients who died of an acute severe attack, the total amount of mucus in the epithelium (i.e. within goblet cells) of both central and peripheral airways was increased by up to 30-fold above that in chronic asthmatic patients or in controls who died of a non-respiratory cause [20, 21]. There was also markedly more mucus in the airway lumina of patients with severe asthma, with increases in the peripheral airways of threefold above the chronic asthmatics and 31-fold above the controls. Thus, goblet cell hyperplasia, particularly in small airways, is associated not only with mucous hypersecretion but also with mortality in asthma. Consequently, it is perceived to be important to understand the mechanisms underlying goblet cell hyperplasia with a view to rationalize inhibitory interventions. To this end, a variety of systems have been developed to model goblet cell hyperplasia in asthma.

Animal models of goblet cell hyperplasia in asthma

Airway goblet cell hyperplasia can be readily induced in animal models of asthma [22]. As in the paper herein by Kasper and colleagues [5], systemic ovalbumin sensitization followed by repeated inhaled ovalbumin challenge in guinea-pigs and rodents results in high blood IgE concentrations and induces inflammatory changes characteristic of asthma, including pulmonary eosinophilia and increased expression of Th2 cytokines [3, 4]. Remodelling includes increased smooth muscle mass, thickening of the sub-basement membrane region and goblet cell hyperplasia. The remodelling is associated with airway hyper-responsiveness to inhaled bronchoconstrictor agents.

Mechanisms of airway goblet cell hyperplasia in models of asthma

Animal models of asthma, predominantly in the mouse, are beginning to delineate the mechanisms underlying development of airway inflammation and goblet cell hyperplasia (Fig. 1) [23, 24]. Th2 cells release IL-4, IL-5, IL-9 and IL-13 which, when overexpressed *in vivo*, will independently induce airway goblet cell hyperplasia. However, only IL-9 directly induces goblet cell hyperplasia and MUC5AC gene expression. The implication of the latter observation is that the other three cytokines induce goblet cell hyperplasia via indirect effects. Neutrophils and activation of epidermal growth factor receptors (EGFR) are required for IL-13-induced goblet cell hyperplasia [25]. EGFR activation initiates intracellular signal transduction pathways involving tyrosine kinase and mitogen-activated protein kinases that lead to increased mucin synthesis and goblet cell production.

Derivation of new goblet cells: multiplication vs. differentiation

The cellular composition of the airway epithelium can alter both by cell division and by differentiation of one cell into another [26]. There are at least eight cell types in the airway epithelium of the conducting airways. In the airways, the basal, surface epithelial serous and Clara cell are considered progenitor cells with the capacity to undergo division followed by differentiation into 'mature' ciliated or secretory cells. In specific experimental conditions, for example exposure to cigarette smoke, goblet cell division contributes to hyperplasia. However, differentiation of non-granulated airway epithelial cells is a major route for production of new goblet cells [14, 25, 26]. In animals, production of goblet cells is usually at the 'expense' of the progenitor cells, most notably serous and Clara cells, which decrease in number as goblet cell numbers increase. Serous-like cells and Clara cells are found in macroscopically normal bronchioles in human lung [27]. Whether there is a reduction in number in asthma is not reported, but merits investigation. Reduction in the relative proportion of serous and Clara cells has pathophysiological significance because they produce a number of anti-inflammatory, immunomodulatory and antibacterial molecules vital to host defence [28, 29]. For example, serous cells produce lysozyme, lactoferrin, secretory IgA, peroxidase and at least two protease inhibitors. Clara cells produce Clara cell 10-kDa protein, also known as uteroglobulin, Clara cell 55-kDa protein, Clara cell tryptase, β -galactoside-binding lectin, possibly a specific phospholipase, and surfactant proteins A, B and D. Thus, the combination of goblet cell hyperplasia, with associated mucous hypersecretion, and reduced host defence seems a disastrous pathophysiological combination, unless compensatory mechanisms are also invoked.

Compensation for airway goblet cell hyperplasia

There is a trend in biology towards balancing homeostatic and pathophysiological processes. Consequently, it might be expected that there would be compensatory mechanisms to balance airway goblet cell hyperplasia. There are now indications that goblet cells produce more than just mucins. For example, sheep airway goblet cells produce in abundance a lactoperoxidase that potently scavenges hydrogen peroxide, an important mediator of oxidative stress and associated inflammation [30, 31]. The anti-inflammatory and immunomodulatory molecule, SP-D, has now been shown to be produced by hyperplastic goblet cells in rat airways [5]. Thus, goblet cell secretions are a combination of mucins and host defence molecules. The implication of this is that the reduced anti-inflammatory 'shield', as a result of goblet cells replacing serous and Clara cells, is compensated for by the increase in host defence molecules in hyperplastic goblet cells (Fig. 1). Interestingly, Kasper and colleagues [5] found that dexamethasone inhibited the pulmonary eosinophilia in the allergic rats without affecting SP-D expression. Corticosteroids also inhibit goblet cell hyperplasia in a variety of animal models [14]. Selective inhibition of pathophysiological events, such as eosinophilia and goblet cell hyperplasia, with retention of expression of host defence molecules such as SP-D, presumably contributes to the anti-inflammatory efficacy of corticosteroids in asthma [32].

Conclusions

Goblet cell hyperplasia is a component of airway remodelling in asthma. Until recently production of mucin was considered the principal function of goblet cells and goblet cell hyperplasia was a purely pathophysiological process. The demonstration that sheep goblet cells produce a lactoperoxidase and that hyperplastic goblet cells in rat airways produce SP-D suggests an anti-inflammatory and immunomodulatory role for goblet cells. Consequently, mere inhibition of airway goblet cell hyperplasia may only be partial therapy in asthma. Corticosteroids reduce goblet cell number but maintain SP-D levels. This indicates that if novel pharmaceutical interventions are to be as successful as corticosteroids in asthma therapy, they will need to balance homeostatic and pathophysiological processes. There is now a need to determine which anti-inflammatory, immunomodulatory and antibacterial mediators are produced by human airway goblet cells, and whether or not these are altered in asthma and other respiratory diseases. This information will increase our understanding of goblet cell physiology and pathophysiology, and rationalize development of pharmaceutical interventions aimed at inhibiting or reversing airway remodelling.

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