Club cells, CC10 and self-control at the epithelial surface

Pieter S. Hiemstra[1] and Arnaud Bourdin[2]

Affiliations: [1]Dept of Pulmonology, Leiden University Medical Center, Leiden, The Netherlands. [2]Dept of Respiratory Diseases, Hôpital Arnaud de Villeneuve, Montpellier, France.

Correspondence: Arnaud Bourdin, CHRU, Respiratory Dept, Hôpital Arnaud de Villeneuve, Montpellier, 34295, France. E-mail: a-bourdin@chu-montpellier.fr

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CC10, at physiological concentrations, may contribute to the maintenance of homeostasis in the peripheral airways http://ow.ly/yQHBy

There has been a recent marked increase in our insight into mechanisms that control inflammation, unwanted immune responses and tissue injury. This is illustrated by the wealth of literature on the role of regulatory T- and B-cells in lung disease, but also by studies on anti-inflammatory cytokines such as interleukin (IL)-10, and products of microbial metabolism such as short-chain fatty acids. The airway epithelium also shows clear signs of self-control, and studies on the club cell 10-kDa protein (CC10; also known as *e.g.* club cell secretory protein or secretoglobin family 1A member 1 (SCGB1A1)) have identified it as one of the mediators involved [1]. CC10 is a main product of club cells, which are especially abundant in the peripheral airways where they contribute to maintenance of airway integrity and repair [2]. The consequences of injury to the small airways are clear from the involvement of small airway dysfunction in an increasing number of lung diseases. Moreover, a defect in the relative abundance of CC10-expressing cells in the peripheral airways of patients with asthma, chronic obstructive pulmonary disease (COPD) and post-transplant obliterative bronchiolitis was reported [3–5]. These observations support an important role for club cells and CC10 in the control of the integrity of these airways and in mediating a swift repair response upon injury. Indeed, several studies indicate that CC10-expressing cells may exert their protective effect in part through their self-renewal and differentiation properties [6]. In addition to CC10, other club cell products may contribute to airway defense against inhaled triggers, such as members of the cytochrome P450 enzyme family that may help to detoxify toxic inhaled substances.

CC10 is a member of the secretoglobin family of small secreted proteins, and has been shown to display anti-inflammatory and immunomodulatory activities [1]. The importance of CC10 is illustrated by studies showing a role for CC10 and polymorphisms in the *SCGB1A1* gene in the pathogenesis of a range of inflammatory lung disorders including asthma and COPD. In addition, knock-out mouse models have revealed the importance of CC10 in maintaining epithelial integrity, although a recent study using smoke exposure failed to show an increased susceptibility in *Scgb1a1*$^{-/-}$ mice [7]. Notably, physiological CC10 expression in mouse airways largely differs from that in humans and, therefore, data from mouse studies of CC10 and club cell function must be interpreted with caution. CC10 readily diffuses from the lung into the systemic circulation and numerous studies have shown it to be a biomarker of increased airway permeability based on increased circulating levels in, for example, smokers [8]. However, expression of CC10 in the lung is decreased as a result of lung injury. Interestingly, reduced serum CC10 was recently shown to be associated with accelerated decline of forced expiratory volume in 1 s in COPD, although the magnitude of the observed association was only limited [7].

One of the main mechanisms involved in the endogenous anti-inflammatory activity of CC10 appears to be its ability to inhibit nuclear factor (NF)-κB activity by suppressing phosphorylation of its inhibitor, IκBα [9].

Received: May 14 2014 | Accepted after revision: July 01 2014

Conflict of interest: None declared.

In this issue of the *European Respiratory Journal*, TOKITA *et al.* [10] provide evidence that CC10 may also inhibit mucus secretion by lipopolysaccharide- or IL-13-exposed human primary bronchial epithelial cells. They cultured these cells at the air–liquid interface to allow mucociliary differentiation, and showed that CC10 at 20 $ng \cdot mL^{-1}$ inhibited secretion and mRNA expression of both the mucin MUC5AC and the neutrophil chemoattractant IL-8/CXCL8. The observation that CC10 inhibited phosphorylation of both NF-κB and extracellular signal-regulated protein kinase 1/2 provided insight into the mechanism of action of CC10, even though there is no known receptor for it. In this way, the authors demonstrated that CC10 not only directly affects production of pro-inflammatory mediators but may also modulate epithelial remodelling [11]. The strengths of the study include the use of primary, well-differentiated bronchial epithelial cells, although cells from only one donor appear to have been used. No information was provided on inter-donor differences or on the sensitivity of airway epithelial cells from specific patient populations to the inhibitory activity of CC10. Therefore, translation of these findings to diseased airways cannot yet be readily made. Finally, future studies using bronchiolar epithelial culture systems representing peripheral airways containing adequate numbers of club cells may provide insight into the physiological role of endogenous CC10 production in the regulation of epithelial remodelling.

The study by TOKITA *et al.* [10] adds to the body of evidence showing that CC10, at physiologically relevant concentrations, may contribute to the maintenance of homeostasis in the peripheral airways. Does this also mean that CC10 is a candidate drug for the treatment of inflammatory lung diseases? Human CC10 can be readily produced in recombinant form and appears to be stable. The results of a small clinical trial have been published, in which recombinant human (rh)CC10 was evaluated in a double-blind, placebo-controlled design [12]. Possibly because of its small sample size, this study failed to show an effect of intranasal administration of rhCC10 on allergen-induced symptoms in seasonal allergic rhinitis. In addition, studies on CC10 administration to premature infants with respiratory distress syndrome have shown promising results without safety issues [13]. Such studies may provide important insight into whether an important endogenous self-regulatory molecule may also serve as an efficient therapeutic agent. As chronic injuries usually underlie chronic inflammatory airway diseases, such treatment should be evaluated on a long-term basis, which is a substantial, but important and interesting, challenge.

References

1 Wang H, Liu Y, Liu Z. Clara cell 10-kD protein in inflammatory upper airway diseases. *Curr Opin Allergy Clin Immunol* 2013; 13: 25–30.
2 Wong AP, Keating A, Waddell TK. Airway regeneration: the role of the Clara cell secretory protein and the cells that express it. *Cytotherapy* 2009; 11: 676–87.
3 Shijubo N, Itoh Y, Yamaguchi T, *et al.* Clara cell protein-positive epithelial cells are reduced in small airways of asthmatics. *Am J Respir Crit Care Med* 1999; 160: 930–933.
4 Pilette C, Godding V, Kiss R, *et al.* Reduced epithelial expression of secretory component in small airways correlates with airflow obstruction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163: 185–194.
5 Bourdin A, Mifsud NA, Chanez B, *et al.* Donor Clara cell secretory protein polymorphism is a risk factor for bronchiolitis obliterans syndrome after lung transplantation. *Transplantation* 2012; 94: 652–658.
6 Gras D, Chanez P, Vachier I, *et al.* Bronchial epithelium as a target for innovative treatments in asthma. *Pharmacol Ther* 2013; 140: 290–305.
7 Park HY, Churg A, Wright JL, *et al.* Club cell protein 16 and disease progression in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013; 188: 1413–1419.
8 Broeckaert F, Clippe A, Knoops B, *et al.* Clara cell secretory protein (CC16): features as a peripheral lung biomarker. *Ann NY Acad Sci* 2000; 923: 68–77.
9 Long XB, Hu S, Wang N, *et al.* Clara cell 10-kDa protein gene transfection inhibits NF-κB activity in airway epithelial cells. *PLoS ONE* 2012; 7: e35960.
10 Tokita E, Tanabe T, Asano K, *et al.* Club cell 10-kDa protein attenuates airway mucus hypersecretion and inflammation. *Eur Respir J* 2014; 44: 1002–1010.
11 Akram KM, Lomas NJ, Spiteri MA, *et al.* Club cells inhibit alveolar epithelial wound repair *via* TRAIL-dependent apoptosis. *Eur Respir J* 2013; 41: 683–694.
12 Widegren H, Andersson M, Greiff L. Effects of Clara cell 10 (CC10) protein on symptoms and signs of allergic rhinitis. *Ann Allergy Asthma Immunol* 2009; 102: 51–56.
13 Levine CR, Gewolb IH, Allen K, *et al.* The safety, pharmacokinetics, and anti-inflammatory effects of intratracheal recombinant human Clara cell protein in premature infants with respiratory distress syndrome. *Pediatr Res* 2005; 58: 15–21.

DOI: 10.1183/09031936.00089214