Received: 28 April 2021 | Accepted: 31 July 2021

DOI: 10.1111/all.15033

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

REVIEW ARTICLE

Secretoglobins in the big picture of immunoregulation in airway diseases

Martine Mootz[1,2,3] | Constanze A. Jakwerth[1,2] | Carsten B. Schmidt-Weber[1,2] | Ulrich M. Zissler[1,2]

[1]Center of Allergy & Environment (ZAUM), Technical University of Munich (TUM) and Helmholtz Center Munich, German Research Center for Environmental Health (HMGU), Munich, Germany

[2]Member of the German Center of Lung Research (DZL), CPC-M, Munich, Germany

[3]Technical University of Munich (TUM), TUM School of Medicine, Klinikum Rechts der Isar, Munich, Germany

Correspondence
Ulrich M. Zissler, Center of Allergy & Environment (ZAUM), Technical University and Helmholtz Center Munich, Biedersteiner Str. 29, 80202 Munich, Germany.
Email: ulrich.zissler@tum.de

Funding information
This study was supported by the German Center for Lung Research (DZL) to UMZ, HG, and CSW; a Grant of the German Research Foundation (DFG) No. 398577603 to CSW and UMZ

Abstract

The proteins of the secretoglobin (SCGB) family are expressed by secretory tissues of barrier organs. They are embedded in immunoregulatory and anti-inflammatory processes of airway diseases. This review particularly illustrates the immune regulation of SCGBs by cytokines and their implication in the pathophysiology of airway diseases. The biology of SCGBs is a complex topic of increasing importance, as they are highly abundant in the respiratory tract and can also be detected in malignant tissues and as elements of immune control. In addition, SCGBs react to cytokines, they are embedded in Th1 and Th2 immune responses, and they are expressed in a manner dependent on cell maturation. The big picture of the SCGB family identifies these factors as critical elements of innate immune control at the epithelial barriers and highlights their potential for diagnostic assessment of epithelial activity. Some members of the SCGB family have so far only been superficially examined, but have high potential for translational research.

KEYWORDS
allergic rhinitis, allergy, asthma, SCGB1A1, Secretoglobin, Th1, Th2

1 | INTRODUCTION

Secretoglobins (SCGBs) are mediators that are produced by the epithelial surfaces and glandular tissues and therefore play an important role in diseases of barrier organs such as the respiratory tract. They are involved in allergic asthma, rhinitis, cystic fibrosis (CF), and chronic obstructive pulmonary disease (COPD). All members of the SCGB family with the exception of SCGB1D2 are expressed in the upper airways[1] and are differentially regulated by inflammatory cytokines.[2] These potentially anti-inflammatory and immunoregulatory mediators are small (10 kDa) secreted proteins that are only expressed in mammals. The evolutionary success of mammals is based on complex epithelial barrier organs, in which SCGBs fulfill complex functions. The aim of this review is to summarize in particular the immunoregulatory functions of SCGBs and their implication in the pathophysiology of airway diseases.

Abbreviations: AIT, allergen-specific immunotherapy; BAL, Bronchoalveolar lavage; BALF, Bronchoalveolar lavage fluid; COPD, Chronic obstructive pulmonary disease; COX2, Cyclooxygenase-2; FEV1, Forced expiratory volume in the first second; FRP2, N-formyl peptide receptor 2; HDM, House dust mite; IFN-γ, Interferon gamma; IgE, Immunoglobulin E; IRDS, Infant respiratory distress syndrome; Lip-1R, Lipocalin-1-receptor; LPS, Lipopolysaccharide; MARCO, Macrophage receptor with collagenous structure; MHCII, Major histocompatibility complex class II; OVA, Ovalbumin; PCR, Polymerase chain reaction; PLA2, Phospholipase A2; RSV, respiratory syncytial virus; SOCS-3, Suppressor of cytokine signaling 3; Th17, T helper 17 cell; TNF-α, Tumor necrosis factor-alpha; VEGF, Vascular endothelial growth factor.

2 | THE SECRETOGLOBIN FAMILY

To date, eleven human genes and five pseudogenes have been identified as members of the SCGB family. They were discovered independently by several groups and have various commonly used names, which are listed in Table 1. SCGBs are located in a cluster on chromosome 11q22.2 through 11q13.1 with the exception of *SCGB3A1* and *SCGB3A2*, which are located on chromosome 5. The entire SCGB family has been genetically linked to several diseases[3,4] in particular, the *SCGB1A1* +38A/G polymorphism has been identified as a risk factor for asthma.[5] A study considering the Korean population suggested that there was a correlation between *SCGB3A2* polymorphisms and asthma, but this remains to be confirmed for other populations.[6]

The eleven members of the human SCGB family are small molecules of about 10 kDa. The basis of the structure is the so-called "globin-fold," which refers to the structure of hemoglobin.[7] It describes a pocket made up of a bundle of eight alpha-helices connected by short loops[8] (Figure 1). The best-studied family member, SCGB1A1, is a homodimer and its two 70-amino acid subunits are linked by disulfide bonds and are arranged antiparallel. Each monomer consists of four α-helices and a β-turn between α-helix-2 and −3, but no β-sheet structure is formed.[9] Due to the dimerization prior to secretion, SCGBs are very resistant to heat, pH, and degradation by proteases. Comparisons of the deduced protein sequence of SCGB2A1 with the amino acid sequences of SCGB2A2 and the other members of the SCGB gene family show that SCGB2A1 is much more similar to SCGB2A2 (58% homology[10]) than to the other members of the gene family.[11] This could be the reason, why these two SCGB family members have redundant functions.

3 | BIOLOGY OF SECRETOGLOBIN FAMILY MEMBERS

SCGB1A1 is the best-studied member of the SCGB family and also one of the most abundant proteins in the lining fluids of the airways. However, the overall role of SCGB1A1 in the context of inflammatory processes is still not thoroughly understood. To give an example, *SCGB1A1* can be used as a damage marker in COPD,[15] as it is induced by acute lung injury.[16,17] In contrast, animal knockout studies[18] and also human gene defects show that *SCGB1A1* is involved in anti-inflammatory functions.[19,20] *SCGB1A1* can be measured in urine, serum, and airway lining fluids and is eliminated by glomerular filtration, almost completely reabsorbed and catabolized by proximal tube cells.[21]

Interestingly, the feline *CH1* gene, known as the allergen *Fel d1* (WHO/IUIS allergen nomenclature), is a member of the SCGB family[22] and its structure is very similar to the one of SCGB1A1. A *Fel d1*-specific IgE reaction occurs in 90–95% of patients with cat allergy. *Fel d1* is found in salivary, perianal, and lacrimal glands and is produced by squamous epithelial cells and sebum glands of cats.[23] This could be of great interest as it is also discussed that *SCGB1A1* is involved in the pathophysiology of allergic diseases. This illustrates the complex functions of this gene family in barrier organs and the need to place SCGBs in the context of organ and disease, which is intended with this review.

Little is known about receptors or molecular mechanisms of the SCGB protein family. However, there are indications that SCGB3A2 binds to the macrophage receptor with collagenous structure (MARCO), a scavenger receptor. Its binding can be inhibited by lipopolysaccharid (LPS) competition.[12] SCGB1A1 has several properties in common with lipocalin-1 and also binds to the lipocalin-1-receptor.[13] The members of the lipocalin family are part of the large class of adipocytokines, which include not only the lipocalins but also retinol-binding proteins, α-microglobulin, β-lactoglobulin, et cetera. However, exact receptors and signaling cascades remain to be determined.[14]

4 | CELLULAR SOURCE OF SECRETOGLOBIN FAMILY MEMBERS

Together with the surfactants, SCGBs represent a prototypical gene family for epithelial cells and are used to define maturation and lineage of this cell type.[24] Interestingly, there are differences in the

TABLE 1 Overview of the commonly used names of the secretoglobin family members

International nomenclature (uniprot)	Commonly used names
SCGB1A1	Secretoglobin family 1A member 1, Clara cell protein, Uteroglobin, CC10, CC16, CCSP, Blastokinin, Clara cell phospholipid-binding protein (CCPBP), Urinary protein 1(UP−1)
SCGB1B3	Secretoglobin family 1B member 3
SCGB1C1	Secretoglobin family 1C member 1, Secretoglobin RYD5
SCGB1D1	Secretoglobin family 1D member 1, Lipophilin A (LIPHA, LPNA)
SCGB1D2	Secretoglobin family 1D member 2, Lipophilin B (LIPHB, LIPN)
SCGB1D4	Secretoglobin family 1D member 4, IIS (Interferon-gamma inducible secretoglobin)
SCGB2A1	Secretoglobin family 2A member 1, Mammoglobin B/2(MGB2, UGB3), Lipophilin C (LIPHC), Lacryglobin
SCGB2A2	Secretoglobin family 2A member 2, Mammoglobin A/1 (MGB1, UBG2)
SCGB2B2	Secretoglobin family 2B member 2, secretoglobin-like protein, SCGBL, SCGB4A2
SCGB3A1	Secretoglobin family 3A member 1, Uteroglobin-related protein 2 (UGRP2), High in normal protein 1, HIN−1, Cytokine HIN−1, Pneumo secretory protein 2 (PnSP−2)
SCGB3A2	Secretoglobin family 3A member 1, Uteroglobin-related protein 1, UGRP1, High in normal protein 2, HIN−2, Pneumo secretory protein 1 (PnSP−1)

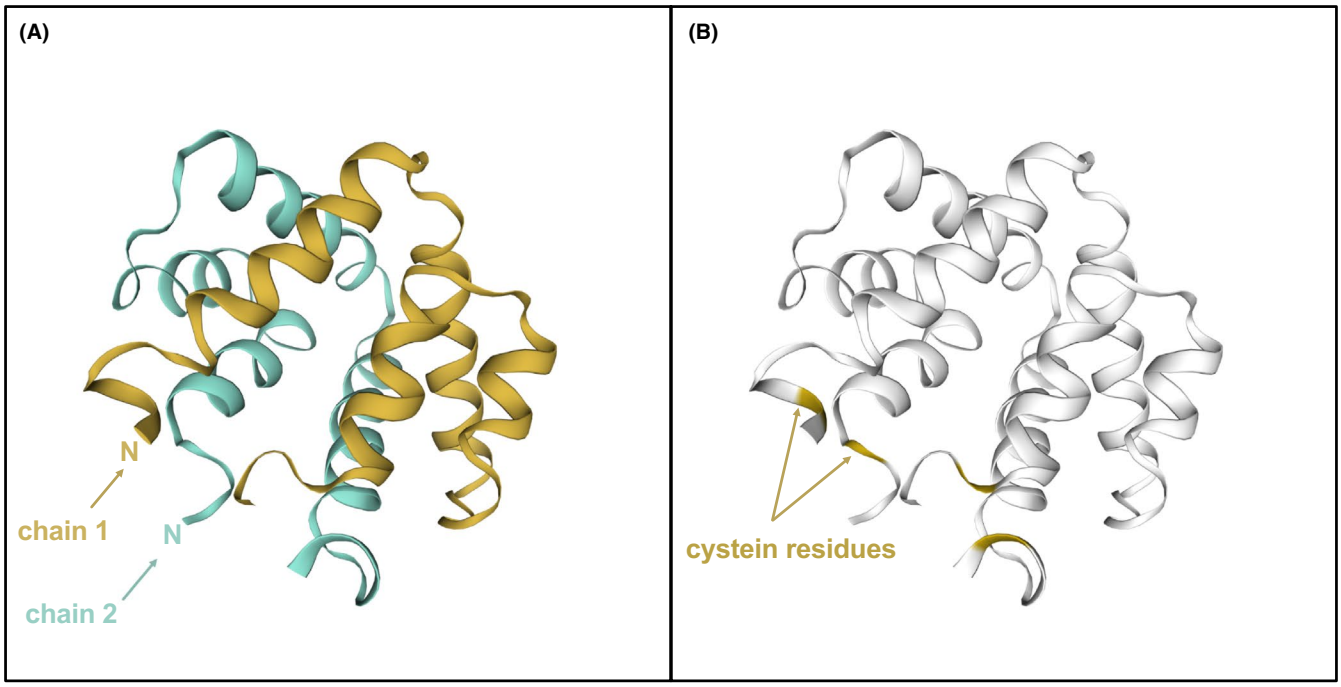

FIGURE 1 Cartoon model of human SCGB1A1 structure extracted from the Uniprot database P11684. Shown are the two homodimers (yellow and blue) in an antiparallel formation (A). Location of cysteine residues is shown in yellow (B). SCGB1A1 has four alpha-helical bundles connected by three loops. The dimers are separated by an interface featuring a cavity formed across two monomers and it enables the binding of hydrophobic ligands as for instance phospholipids, steroids, and various inflammation mediators[9,108]

spatiotemporal expression of *SCGB1A1*, *SCGB3A1*, and *SCGB3A2* during embryogenesis in mice. *SCGB3A2* is expressed early in embryogenesis, both in small and large airways, while *SCGB1A1* is only expressed in later embryogenesis. Furthermore, *SCGB3A1* is only expressed in large airways over the same time period as *SCGB1A1*, suggesting unique functions for each protein.[25]

We know that club cells, formerly known as Clara cells, are the main producers of SCGB1A1. Alveolar type II cells are derived from the club cells and could also produce SCGB1A1. Since alveolar type II cells also produce surfactant protein, it is possible that there is a relation between the two proteins. SCGB1A1 may even protect surfactant from the hydrolysis by phospholipase 2 (PLA2)[26] and therefore plays an important role in supplying the lower airways with surfactant proteins.[27] Pulmonary surfactant is a complex mixture of phospholipids, neutral lipids, and proteins that maintain airway patency by lowering alveolar surface tension.[28] In addition, PLA2 can hydrolyze the phospholipids and reduce the patency of the airways.

Epithelial cells are the main producers of SCGB1A1, for example in the upper airways, endometrium, prostate, and other secretory tissues. In the lung, putative stem cells, airway progenitor cells, and niche-localized stem cells are discussed as additional SCGB1A1 producers in addition to club cells.[24] It has been shown that, in the uterus, the endometrium can produce SCGB1A1, when stimulated with progesterone, a process triggered via the progesterone receptor.[29] In the male prostate, however, SCGB1A1 is constitutively produced.[30] In addition, subpopulations of bone marrow cells seem to be able to produce SCGB1A1[31] and there is also evidence of an association of SCGB1A1 with alveolar macrophages.[24] *SCGB1A1* gene expression has been detected in human alveolar macrophages using real-time PCR in all subjects.[32,33] Recently, we showed that SCGB1A1 is also produced by lymphocytes.[34] In addition, the human protein atlas indicates many cell types that appear to produce SCGB1A1, such as muscle cells and keratinocytes.[35] However, there is a lack of prospective evidence to confirm these screening results. For the other SCGB family members, several cellular sources have been identified in almost all tissues, which are summarized in Table 2.

5 | SECRETOGLOBINS IN DISEASES OF THE UPPER AND LOWER AIRWAYS

The SCGB family is involved in many diseases of the upper and lower airways.[36-38] In this review, we collected literature on acute (allergic rhinitis and common cold) and chronic airway diseases (allergic asthma, COPD, and cystic fibrosis). With regard to upper airway diseases, recent studies have mainly focused on SCGB1A1. In general, SCGB1A1 levels are decreased in patients with inflammatory diseases of the upper airways compared to healthy controls.[39,40]

5.1 | Acute respiratory diseases

Viral infections have an impact on SCGB1A1 levels: urine levels of SCGB1A1 are elevated in infants with acute bronchiolitis[41] and also

TABLE 2 Overview of cell types and tissues expressing the different secretoglobin family members

		SCGB1A1	SCGB1B3	SCGB1C1	SCGB1D1	SCGB1D2	SCGB1D4	SCGB2A1	SCGB2A2	SCGB2B2	SCGB3A1	SCGB3A2	References
Different cell types expressing the secretoglobin family members													
Myeloid originated cells	Monocytes	X									X	X	35
	Macrophages	X									X	X	35
	Granulocytes	X		X						X	X	X	35,130
	Dendritic cells						?				X		35
Lymphatic originated cells	B cells							X					34,35
	T cells	X									X		34,35
	NK cells											X	34,35
Mesenchymal cells	Epithelial cells	X	X	X	X	X	X	X	X	X	X	X	35
	Muscle cells	X			X	X			X	X	X		35,130
Different tissues expressing the secretoglobin family members													
Respiratory tract	X		X	X		X	X	X	X	X	X	1,35,130	
Female tissues	Breast tissue	?		?	?	X		X	X		X	?	35,112,130
	Reproductive system	X		?	X	X	X	X	X		?	?	35,118,130,131
Male tissues	prostate	X			?	X		?	?		X	?	35,130
	Reproductive system	?		?	X	?	X	X	?	X	?	?	35,130
Glands	salivary	?		?	?	X		?	?		X		4,35,130
	lacrimal							X					132
	pituitary	?		?	?	?							35,130
Bone marrow & lymphatic tissues		X		X	X	?	?	X	?	?	?		35,130
Blood		X		X	?	?	?	?	?	X	X	X	35,130
Gastrointestinal system		?		X	?	?		X	?	X	X	?	35,130
Cardiovascular system		?		?	?	X		?	?	?	?	?	35,130
Skin		X			?	X		?	?	X	X		35,130
Kidney and urinary tract		?		?		X		?		?	?		35,130

?: there are indications, that the protein is expressed in those tissues, but need further confirmation; X: expression of the protein in the tissue.

children infected with respiratory syncytial virus (RSV) show elevated serum levels of the protein.[42] The susceptibility for viral infections may depend on the patient's serum SCGB1A1 levels: a study including elite athletes associated lower serum SCGB1A1 levels with a higher susceptibility to viral infections.[43] In contrast to the systemic SCGB1A1 levels, the SCGB1A1 concentration in nasopharyngeal aspirates was lower than in healthy controls and correlated negatively with the severity.[44] The increased levels of the protein in both urine and serum, but decreased levels in nasopharyngeal fluids, could be the result of viral damage to the epithelial barrier and increased leakage to the periphery. Interestingly, *SCGB1A1* knockout mice show more severe lung inflammation after an adenovirus infection,[45] which suggests a protective role for SCGB1A1.

As mentioned above, fewer studies have focused on other SCGBs, but it has been shown that SCGB1C1 is also important for the protection of lung epithelial cells: It recognizes and removes pathogens from the airway mucosa.[46] It also seems to be involved in the development of a common cold.[1,46,47] Elite athletes appear to be more prone to upper airway infections and expression of serum SCGB1C1. Thus, SCGB1C1 could serve as a parameter for susceptibility to respiratory infections, as described for SCGB1A1.[43,47]

Similar to viral infections, patients with allergic rhinitis have decreased levels of SCGB1A1 in the nasal fluid: children with birch pollen allergy show decreased levels of SCGB1A1 in the nasal fluid during and out of birch pollen season compared to healthy controls.[48] In addition, it has been shown in patients with intermittent[49] and persistent[38] allergic rhinitis that the SCGB1A1 levels in nasal fluid within one hour after allergen challenge correlate inversely with the symptoms of rhinitis. To the best of our knowledge, the role of other SCGBs in allergic rhinitis has not yet been described.

5.2 | Chronic respiratory diseases

Asthma patients show lower serum SCGB1A1 levels than healthy controls regardless of whether the diagnosis was topic, atopic, refractory, or non-refractory asthma.[43,50-52] This suggests a different picture than in acute diseases, in which the serum *SCGB1A1* levels are increased. The SCGB1A1 levels in bronchoalveolar lavage fluids (BALF)[50] as well as in the urine[53] of children with asthma were also lower compared to healthy controls. Additionally, lower serum SCGB1A1 levels appear to be associated with a longer disease duration,[54,55] but there was no evidence of an association with severity.[54] In severe asthma, both the SCGB1A1 level and the surfactant protein D level correlate with remodeling indices, suggesting that the proteins are involved in the repair processes.[52] Club cell-positive epithelial cells are also reduced in small airways[56] of patients with asthma, which is one possible explanation for the reduced SCGB1A1 levels.

Conflicting results have been reported for frequently used asthma drugs: on the one hand, budesonide increases the number of club cells, but not the SCGB1A1 content in BALF.[57] Dexamethasone, on the other hand, decreases mucus production by the club cells and also decreases SCGB1A1 levels, either by reducing the number of club cells or by inhibiting SCGB1A1 secretion.[58] Again, this evidence focuses on SCGB1A1, while little information is available on the implication of other SCGBs in disease. It is known, however, that the SCGB3A2 sputum levels are increased in asthma and rhinitis compared to healthy controls.[59]

SCGB1A1 has also been intensively studied in context of COPD, which, like asthma, is also an obstructive pulmonary disease, in which SCGB1A1 levels correlate inversely with the disease severity (lower levels are associated with higher severity).[60] Serum, sputum, and BALF SCGB1A1 levels in COPD patients and smokers are lower than in healthy, non-smoking controls.[36,39,40,61] Unsurprisingly, lower SCGB1A1 levels have been associated with rapid FEV1 deterioration.[62] Serum SCGB1A1 levels were also associated with the risk of COPD progression.[63] A potentially protective role of SCGB1A1 for lung tissue[17,64] has also been suggested in COPD: SCGB1A1 reduces both airway inflammation and smoking-induced decline in lung function, which are the most important pathogenic markers for COPD.[60] This protective effect is also observed upon early intervention with recombinant SCGB1A1, as it upregulates surfactant protein and VEGF expression in infants with respiratory distress syndrome (IRDS).[64]

In contrast to asthma and COPD, recurrent, exacerbative infections are one of the key problems in cystic fibrosis. Decreased SCGB1A1 sputum levels are associated with exacerbation[65] and more intense airway inflammation.[66] Since *Pseudomonas aeruginosa* is one of the most common pathogens in cystic fibrosis, the negative correlation of sputum SCGB1A1 levels with pathogen loads indicates the protective role of the protein in pro-inflammatory diseases.[65,67] In addition to SCGB1A1, SCGB3A1 is also significantly downregulated in sputum.[68]

Overall, these findings suggest an anti-inflammatory function of SCGB1A1. It appears that SCGB1A1 is decreased in local airway inflammation in both acute and chronic diseases, but the serum levels are only increased in acute and not in chronic airway diseases. This discrepancy may result from differences in epithelial permeability in acute viral infections (damage to the epithelial barrier) as opposed to chronic airway diseases, which are associated with thickened, remodeled epithelial barriers.

6 | CURRENT STATUS OF SECRETOGLOBINS AS BIOMARKERS

The members of the SCGB family are easily accessible, chemically stable, and abundant in several biomatrices (serum, BALF, nasopharyngeal fluids, urine, exhaled breath condensate[69]). Since they can be detected in many secretory tissues, they have a high potential as biomarkers for diagnostic and prognostic assessment as well as for therapy monitoring. SCGB1A1 has been proposed as a predictive marker for the risk of impaired lung function,[15,70] determination of COPD severity,[36,36,60,62,63] lung epithelium damage in asthma[50] and might serve as a diagnostic parameter for acute respiratory distress syndrome.[71] In induced sputum from patients with allergic rhinitis, SCGB1A1 levels

increase after allergen-specific immunotherapy (AIT),[34] which may qualify SCGB1A1 as a marker for therapy monitoring.

The role of this protein family as a biomarker has not only been investigated in the context of inflammatory airway diseases, but the members of the SCGB family generally play an important role in malignant diseases and can also be of potential use in oncology (Supplemental Table 1).

7 | SECRETOGLOBINS AND IMMUNE REGULATION

7.1 | General anti-inflammatory mechanisms

The therapeutic application of recombinant SCGB1A1, either via intravenous or intratracheal injection, reduced inflammation in several experimental disease models (obliterative bronchiolitis,[72] infant respiratory distress syndrome,[64] damage from mechanical ventilation,[73] acute lung injury[16,17]). In addition, supplementation of exogenous SCGB1A1 may reduce the elevated pro-inflammatory cytokines and inflammatory build-up caused by *SCGB1A1* germline deficiency.[74] SCGB1A1 supports repair processes and preserves the function of surfactants, while it also has a modulating effect on the surfactant metabolism.[15] In a recent study, we have shown that AIT induces local SCGB1A1 expression after three years of therapy, which co-insides with a reduction in allergic inflammation.[34] In addition, SCGB1A1 renders its anti-inflammatory potential by inhibiting monocyte and neutrophil chemotaxis.[75-78] The family of powerful chemotactic factors for neutrophils (fMLP) mediates chemoattraction via a family of G protein-coupled receptors (formyl peptide receptors, *FRP*). SCGB1A1 binds to FRP2, thereby inhibiting the chemotactic attraction of neutrophils.[78] These findings demonstrate the anti-inflammatory effects of SCGB1A1 and suggest that SCGB1A1 influences immunoregulatory responses.

7.2 | Secretoglobins and the innate immune system

Further evidence suggests that SCGB1A1 interacts with CXCL8 (IL-8), a pro-inflammatory chemokine that attracts neutrophils and is produced by many immune and mesothelial structural cells including epithelial cells, endothelial cells, fibroblasts, macrophages, and granulocytes. In this context, two mechanisms have been described: A) where SCGB1A1 is able to bind IL-8 directly, thereby reducing airway neutrophilia[20] and B) where SCGB1A1 inhibits airway epithelial cells from producing IL-8—although the receptors have not been examined in detail. This could be important for COPD patients, as they express higher IL-8 levels than healthy controls,[75] but also for children with cystic fibrosis, in whom SCGB1A1 correlates negatively with IL-8 levels and the severity of the inflammatory processes.[76] The anti-inflammatory effect of SCGB1A1 on neutrophils is not limited to IL-8, but also modulates neutrophil migration via other chemokines and their receptors (CXCR1 and CXCR2).[79]

In addition, SCGB1A1 mediates the regulation of the innate immune system via dendritic cells, by inhibiting their ability to mobilize T helper 17 (Th17) cells in an OVA-induced allergic rhinitis model.[80] Furthermore, mice lacking SCGB1A1 have strongly reduced cytokine and chemokine responses in the alveolar milieu.[81] Activation of the innate immune system by LPS has been studied with respect to both SCGB1A1 and SCGB3A2. Inhalation of LPS increases SCGB1A1 levels in the blood and decreases SCGB1A1 levels in airway fluids, likely by modifying the permeability of the airway epithelia.[82] Interestingly, pretreatment with prednisolone inhibited the SCGB1A1 response to LPS-induced airway inflammation, potentially by controlling vascular leakage.[83] Tumor necrosis factor-alpha (TNF-α), in turn, increases SCGB1A1 levels in BEAS-2B bronchial epithelial cells.[84]

Interestingly, SCGB1A1 also interacts with fibronectin, an extracellular matrix protein that has been described to form complexes with IgA and to accumulate in the kidney when SCGB1A1 levels were decreased. Reconstitution of SCGB1A1 inhibits the formation of these complexes between fibronectin and IgA[85] and prevents glomerulopathy in mice.[85,86] Furthermore, SCGB1A1 prevents the deposition of fibronectin not only in the lung but also in the kidney.[87] In contrast to SCGB1A1, SCGB3A2 inhibits LPS-induced airway inflammation along with the LPS-triggered expression of *TNF-α* and also of *CXCL8*.[88]

In conclusion, the anti-inflammatory function of SCGB1A1 becomes evident as it inhibits CXCL8 and modifies the activity of dendritic and epithelial cells.

7.3 | Secretoglobins and the type-1 adaptive immune response

Similar to TNF-α, IFN-γ induces *SCGB1A1* expression, also via JAK-STAT pathways.[89,90] IFN-γ is produced by Th1 cells after T-cell receptor activation and plays an important role in the induction of MHC class II molecules and thus of antigen presentation, which is essential for the cellular response to infections. IFN-γ also interferes with other members of the SCGB family, however, unlike *SCGB1A1*, IFN-γ downregulates the gene expression of *SCGB3A1*.[91] It induces phosphorylation of and thereby activation of STAT1, which leads to the inhibition of the promoter activity of the *SCGB3A1 gene*.[91] Taken together, IFN-γ has different effects on the members of the SCGB family: it stimulates the production of SCGB1A1[92] and SCGB3A2 while inhibiting SCGB3A1.[91]

7.4 | Secretoglobins and the type-2-mediated immune response

Our work and that of others have shown that in type-2 diseases such as allergic rhinitis, the expression of *SCGB1A1* is downregulated, while

TABLE 3 Overview of the impacts of Th1 and Th2 cytokines, common inflammatory mediators, and mediators of the innate immune system on secretoglobin expression

Regulation SCGBs	Adaptive immune system				Common inflammatory mediators	Innate immune system		
	Th1	Th2						
Mediators	IFN-γ	IL-4	IL-5	IL-13	IL-10	TNF-α	LPS	References
SCGB1A1	▲[a]	▼		▼		▲	▼[b]	19,48,82-84,89
SCGB1B3								
SCGB1C1	▼	▲		▲				2
SCGB1D1	▼					▲		2
SCGB1D2								
SCGB1D4	▲	▼		▼		▲		2,89
SCGB2A1	▼	▲		▲		▲		2
SCGB2A2	▲					▲		2
SCGB2B2								
SCGB3A1	▼[a]	▲		▲				2,91,107
SCGB3A2	▲	▼	▼	▼	▲		▼	2,92,106,128,129

We have preliminary data that does not confirm the upregulation of SCGB1A1 and downregulation of SCGB3A1 through IFN-γ stimulation.

▲, Cytokine induces expression of the SCGB.

▼, Cytokine downregulates the expression of the SCGB.

[a] We have preliminary data not confirming these findings.

[b] After LPS treatment, SCGB1A1 levels decrease in airway fluids but increase in blood.

allergen-specific immunotherapy induces the expression of *SCGB1A1* in the upper and lower airways.[34,48] In general, it is believed that AIT suppresses Th2 immune responses and SCGB1A1 may contribute to this effect, as it was previously described that SCGB1A1 suppresses osteopontin,[93] a cytokine with Th2-promoting functions.[94]

Since SCGB1A1 appears to play a role in type-2 immune regulation, the question arises as to which signaling pathways trigger the *SCGB1A1* promoter. The transcription factors *FOXA1*, also known as hepatocyte nuclear factor 3, and *FOXA2* induce *SCGB1A1* expression.[95-98] Reduced SCGB1A1 levels in asthma are attributed to a lack of *FOXA2* expression.[19] Th2 cytokines such as IL-4, IL-9, and IL-13 inhibit *FOXA2* and can thereby limit *SCGB1A1* mRNA expression. *SCGB1A1*, in turn, inhibits Th2 immune response not only by downregulating *FOXA2*, but also of *SOCS-3* expression.[78] *SOCS-3* plays an important role in initiating and maintaining the Th2-mediated immune response.[99]

SCGB1A1 also binds Ca^{2+}, a cofactor of phospholipase A2 (*PLA2*), and thereby inhibits PLA2 activity,[100] which is at the beginning of synthesis of type-2 immunity-associated lipid mediators (arachidonic acids).[101] PLA2 can damage the membrane of alveolar cells directly and is correlated with lung injury.[102,103] In addition, SCGB1A1 suppresses *COX2* gene expression, which is a key enzyme in the synthesis of lipid mediators.[104]

Like SCGB1A1, SCGB3A2 appears to play an important role in the immune regulation of the upper airways. *SCGB3A2* knockout shows exacerbated airway inflammation after exposure to house dust mites (HDM).[105] Consistent with these findings, *in vitro* studies and experimental asthma mouse models, show that IL-4, IL-5, and IL-13 or allergen challenge downregulate *SCGB3A2* mRNA expression.[2,106] In contrast to the inhibition of SCGB3A2 by type-2 cytokines, IL-4 and IL-13 have been reported to induce *SCGB3A1* expression via the binding of STAT6 to a *SMAD* binding element (*SBE*) in the *SCGB3A1* promoter.[107] For an overview of the regulation of SCGBs by cytokines, view Table 3 and Figure 2.

In summary, SCGBs are differentially regulated by type-2 cytokines and show immunomodulatory functions. Further research is needed on the role of SCGBs other than SCGB1A1.

8 | FINAL REMARKS

Overall, the SCGB family mediates important functions at the epithelial barrier, is integrated into the immune response, and provides interesting targets for diagnosis and therapy. Even though there is substantial knowledge on SCGB1A1, the other family members are open for new discoveries.

At the clinical level, SCGB1A1 is tremendously abundant in the respiratory tract and is easily accessible in nasal secretions, induced sputum,[34] or urine.[74] Its function as a lung protector is well established[100] and of particular interest. SCGB1A1 may also serve as a potential biomarker for lung tissue damage in COPD[60] or following mechanical ventilation.[53] In cystic fibrosis and asthma, lower SCGB1A1 levels are associated with exacerbation levels[65] and longer disease duration,[54] respectively.

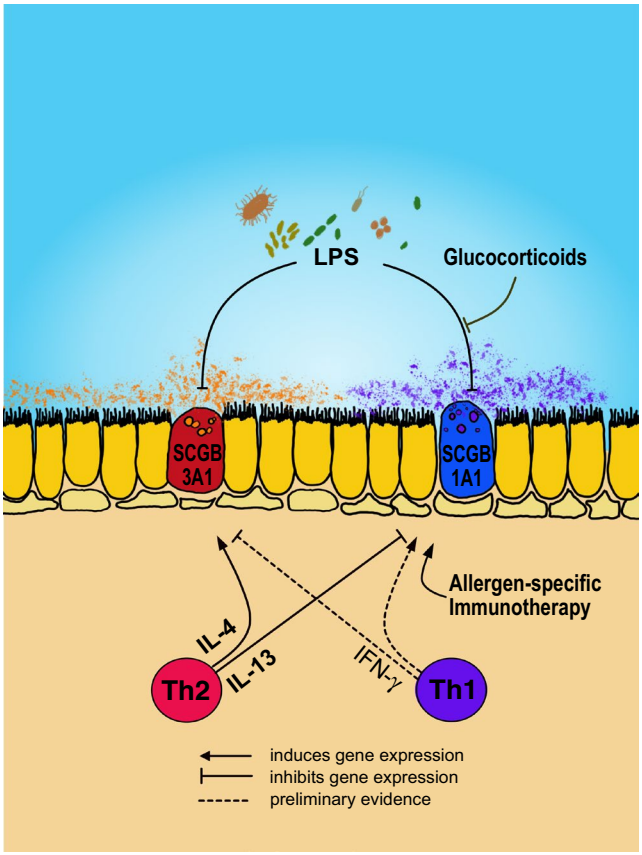

FIGURE 2 Schematic overview of the effects of Th1 and Th2 cytokines, LPS, corticosteroids, and allergen-specific immunotherapy on SCGB1A1 and SCGB3A1 expression of airway epithelial cells. While the impact of Th2 cytokines on SCGB1A1 and SCGB3A1 expression has been demonstrated by multiple groups, the effects of Th1 cytokines need further investigations (dashed line). Our preliminary data do not match this finding

At the mechanistic level, epithelial-derived SCGB1A1 has anti-inflammatory properties and is reduced at local inflammation sites in both type-2 diseases, asthma, and allergic rhinitis.[39,40] The overall view shows a differential expression of the SCGB family members with respect to adaptive (IFN-γ, IL-4, IL-5, and IL-13) as well as innate (TNF-α) cytokines. Future studies are required to substantiate the role of SCGB family members, in particular, in the context of their antagonistic regulation by innate and adaptive cytokines.

ACKNOWLEDGMENTS

We thank Mrs. Sara Ryan for linguistic proofreading and her helpful comments.

CONFLICT OF INTEREST

CSW received support for research projects from PLS Design, LETI, Zeller AG, and Allergopharma and accepted honoraria for consultancy and seminars from LETI and Allergopharma. CSW also received travel support from EAACI. UMZ received payment for manuscripts from Deutsches Aerzteblatt and funds for travel from the European Academy of Allergy and Clinical Immunology (EAACI) and Collegium Internationale Allergologicum (CIA). MM and CAJ declare that they have no relevant conflict of interest.

AUTHOR CONTRIBUTIONS

All authors involved in literature search and writing.

ORCID

Carsten B. Schmidt-Weber https://orcid.org/0000-0002-3203-8084
Ulrich M. Zissler https://orcid.org/0000-0003-4826-3419

REFERENCES

1. Jackson BC, Thompson DC, Wright MW, et al. Update of the human secretoglobin (SCGB) gene superfamily and an example of 'evolutionary bloom' of androgen-binding protein genes within the mouse Scgb gene superfamily. *Hum Genom*. 2011;5(6):691-702.
2. Lu X, Wang N, Long XB, You XJ, Cui YH, Liu Z. The cytokine-driven regulation of secretoglobins in normal human upper airway and their expression, particularly that of uteroglobin-related protein 1, in chronic rhinosinusitis. *Respir Res*. 2011;12:28.
3. Niimi T, Munakata M, Keck-Waggoner CL, et al. A polymorphism in the human UGRP1 gene promoter that regulates transcription is associated with an increased risk of asthma. *Am J Hum Genet*. 2002;70(3):718-725.
4. Niimi T, Copeland NG, Gilbert DJ, et al. Cloning, expression, and chromosomal localization of the mouse gene (Scgb3a1, alias Ugrp2) that encodes a member of the novel uteroglobin-related protein gene family. *Cytogenet Genome Res*. 2002;97(1–2):120-127.
5. Nie W, Xue C, Chen J, Xiu Q. Secretoglobin 1A member 1 (SCGB1A1) +38A/G polymorphism is associated with asthma risk: a meta-analysis. *Gene*. 2013;528(2):304-308.
6. Kim SK, Seok H, Park HJ, et al. Association between secretoglobin family 3A member 2 (SCGB3A2) gene polymorphisms and asthma in a Korean population. *Med Sci Monit*. 2017;23:1880-1885.
7. Callebaut I, Poupon A, Bally R, et al. The uteroglobin fold. *Ann N Y Acad Sci*. 2000;923:90-112.
8. Singh G, Katyal SL, Brown WE, Kennedy AL, Singh U, Wong-Chong ML. Clara cell 10 kDa protein (CC10): comparison of structure and function to uteroglobin. *Biochim Biophys Acta*. 1990;1039(3):348-355.
9. Pattabiraman N, Matthews JH, Ward KB, Mantile-Selvaggi G, Miele L, Mukherjee AB. Crystal structure analysis of recombinant human uteroglobin and molecular modeling of ligand binding. *Ann N Y Acad Sci*. 2000;923:113-127.
10. Becker RM, Darrow C, Zimonjic DB, Popescu NC, Watson MA, Fleming TP. Identification of mammaglobin B, a novel member of the uteroglobin gene family. *Genomics*. 1998;54(1):70-78.
11. Bellone S, Tassi R, Betti M, et al. Mammaglobin B (SCGB2A1) is a novel tumour antigen highly differentially expressed in all major histological types of ovarian cancer: implications for ovarian cancer immunotherapy. *Br J Cancer*. 2013;109(2):462-471.
12. Bin LH, Nielson LD, Liu X, Mason RJ, Shu HB. Identification of uteroglobin-related protein 1 and macrophage scavenger receptor with collagenous structure as a lung-specific ligand-receptor pair. *J Immunol*. 2003;171(2):924-930.
13. Zhang Z, Kim SJ, Chowdhury B, et al. Interaction of uteroglobin with lipocalin-1 receptor suppresses cancer cell motility and invasion. *Gene*. 2006;369:66-71.
14. Flower DR. Beyond the superfamily: the lipocalin receptors. *Biochim Biophys Acta*. 2000;1482(1–2):327-336.
15. Braido F, Riccio AM, Guerra L, et al. Clara cell 16 protein in COPD sputum: a marker of small airways damage? *Respir Med*. 2007;101(10):2119-2124.

16. McAuley DF, Matthay MA. Clara cell protein CC16. A new lung epithelial biomarker for acute lung injury. *Chest*. 2009;135(6):1408-1410.
17. Kropski JA, Fremont RD, Calfee CS, Ware LB. Clara cell protein (CC16), a marker of lung epithelial injury, is decreased in plasma and pulmonary edema fluid from patients with acute lung injury. *Chest*. 2009;135(6):1440-1447.
18. Laucho-Contreras ME, Polverino F, Rojas-Quintero J, Wang X, Owen CA. Club cell protein 16 (Cc16) deficiency increases inflamm-aging in the lungs of mice. *Physiol Rep*. 2018;6(15):e13797.
19. Zhu L, An L, Ran D, et al. The club cell marker SCGB1A1 downstream of FOXA2 is reduced in asthma. *Am J Respir Cell Mol Biol*. 2019;60(6):695-704.
20. Knabe L, Petit A, Vernisse C, et al. CCSP counterbalances airway epithelial-driven neutrophilic chemotaxis. *Eur Respir J*. 2019;54(1):1802408.
21. Martin-Granado A, Vazquez-Moncholi C, Luis-Yanes MI, Lopez-Mendez M, Garcia-Nieto V. Determination of Clara cell protein urinary elimination as a marker of tubular dysfunction. *Pediatr Nephrol*. 2009;24(4):747-752.
22. Klug J, Beier HM, Bernard A, et al. Uteroglobin/Clara cell 10-kDa family of proteins: nomenclature committee report. *Ann N Y Acad Sci*. 2000;923:348-354.
23. Kaiser L, Gronlund H, Sandalova T, et al. The crystal structure of the major cat allergen Fel d 1, a member of the secretoglobin family. *J Biol Chem*. 2003;278(39):37730-37735.
24. Kim CF, Jackson EL, Woolfenden AE, et al. Identification of bronchioalveolar stem cells in normal lung and lung cancer. *Cell*. 2005;121(6):823-835.
25. Naizhen X, Kido T, Yokoyama S, Linnoila RI, Kimura S. Spatiotemporal expression of three secretoglobin proteins, SCGB1A1, SCGB3A1, and SCGB3A2, in Mouse Airway Epithelia. *J Histochem Cytochem*. 2019;67(6):453-463.
26. Guy J, Dhanireddy R, Mukherjee AB. Surfactant-producing rabbit pulmonary alveolar type II cells synthesize and secrete an antiinflammatory protein, uteroglobin. *Biochem Biophys Res Commun*. 1992;189(2):662-669.
27. ter Horst SA, Fijlstra M, Sengupta S, Walther FJ, Wagenaar GT. Spatial and temporal expression of surfactant proteins in hyperoxia-induced neonatal rat lung injury. *BMC Pulm Med*. 2006;6:8.
28. Hite RD, Grier BL, Waite BM, et al. Surfactant protein B inhibits secretory phospholipase A2 hydrolysis of surfactant phospholipids. *Am J Physiol Lung Cell Mol Physiol*. 2012;302(2):L257-265.
29. Muller-Schottle F, Classen-Linke I, Alfer J, et al. Expression of uteroglobin in the human endometrium. *Mol Hum Reprod*. 1999;5(12):1155-1161.
30. Peri A, Cordella-Miele E, Miele L, Mukherjee AB. Tissue-specific expression of the gene coding for human Clara cell 10-kD protein, a phospholipase A2-inhibitory protein. *J Clin Invest*. 1993;92(5):2099-2109.
31. Bustos ML, Mura M, Marcus P, et al. Bone marrow cells expressing clara cell secretory protein increase epithelial repair after ablation of pulmonary clara cells. *Mol Ther*. 2013;21(6):1251-1258.
32. Willey JC, Coy E, Brolly C, et al. Xenobiotic metabolism enzyme gene expression in human bronchial epithelial and alveolar macrophage cells. *Am J Respir Cell Mol Biol*. 1996;14(3):262-271.
33. Reynolds SD, Reynolds PR, Snyder JC, Whyte F, Paavola KJ, Stripp BR. CCSP regulates cross talk between secretory cells and both ciliated cells and macrophages of the conducting airway. *Am J Physiol Lung Cell Mol Physiol*. 2007;293(1):L114-123.
34. Zissler UM, Jakwerth CA, Guerth F, et al. Allergen-specific immunotherapy induces the suppressive secretoglobin 1A1 in cells of the lower airways. *Allergy* 2021;76(8):2461–2474.
35. https://www.proteinatlas.org.
36. Rong B, Fu T, Gao W, et al. Reduced serum concentration of CC16 is associated with severity of chronic obstructive pulmonary disease and contributes to the diagnosis and assessment of the disease. *Int J Chron Obstruct Pulmon Dis*. 2020;15:461-470.
37. Zhai J, Insel M, Addison KJ, et al. Club cell secretory protein deficiency leads to altered lung function. *Am J Respir Crit Care Med*. 2019;199(3):302-312.
38. Kim SI, Kwon OE, Park JM, et al. Correlation of nasal fluid biomarkers and symptoms in patients with persistent allergic rhinitis. *Ann Otol Rhinol Laryngol*. 2020;129(6):542-547.
39. Bernard A, Roels H, Buchet JP, Lauwerys R. Decrease of serum Clara cell protein in smokers. *Lancet*. 1992;339(8809):1620.
40. Shijubo N, Itoh Y, Yamaguchi T, et al. Serum and BAL Clara cell 10 kDa protein (CC10) levels and CC10-positive bronchiolar cells are decreased in smokers. *Eur Respir J*. 1997;10(5):1108-1114.
41. Egron C, Labbe A, Rochette E, Mulliez A, Bernard A, Flore A. Urinary club cell protein 16 (CC16): utility of its assay during acute bronchiolitis. *Pediatr Pulmonol*. 2020;55(2):490-495.
42. Johansson S, Kristjansson S, Bjarnarson SP, Wennergren G, Rudin A. Clara cell protein 16 (CC16) serum levels in infants during respiratory syncytial virus infection. *Acta Paediatr*. 2009;98(3):579-581.
43. Kurowski M, Jurczyk J, Jarzebska M, et al. Association of serum Clara cell protein CC16 with respiratory infections and immune response to respiratory pathogens in elite athletes. *Respir Res*. 2014;15:45.
44. Yu G, Mo S, Gao L, et al. Club cell 10-kDa protein (CC10) inhibits cPLA2/COX2 pathway to alleviate RSV-induced airway inflammation and AHR. *Int Immunopharmacol*. 2020;83:106327.
45. Harrod KS, Mounday AD, Stripp BR, Whitsett JA. Clara cell secretory protein decreases lung inflammation after acute virus infection. *Am J Physiol*. 1998;275(5):L924-930.
46. Dear TN, Boehm T, Keverne EB, Rabbitts TH. Novel genes for potential ligand-binding proteins in subregions of the olfactory mucosa. *EMBO J*. 1991;10(10):2813-2819.
47. Orysiak J, Malczewska-Lenczowska J, Bik-Multanowski M. Expression of SCGB1C1 gene as a potential marker of susceptibility to upper respiratory tract infections in elite athletes - a pilot study. *Biol Sport*. 2016;33(2):107-110.
48. Johansson S, Keen C, Stahl A, Wennergren G, Benson M. Low levels of CC16 in nasal fluid of children with birch pollen-induced rhinitis. *Allergy*. 2005;60(5):638-642.
49. Benson M, Fransson M, Martinsson T, Naluai AT, Uddman R, Cardell LO. Inverse relation between nasal fluid Clara Cell Protein 16 levels and symptoms and signs of rhinitis in allergen-challenged patients with intermittent allergic rhinitis. *Allergy*. 2007;62(2):178-183.
50. Guerra S, Vasquez MM, Spangenberg A, Halonen M, Martin RJ. Club cell secretory protein in serum and bronchoalveolar lavage of patients with asthma. *J Allergy Clin Immunol*. 2016;138(3):932-934 e931.
51. Van Vyve T, Chanez P, Bernard A, et al. Protein content in bronchoalveolar lavage fluid of patients with asthma and control subjects. *J Allergy Clin Immunol*. 1995;95(1 Pt 1):60-68.
52. Emmanouil P, Loukides S, Kostikas K, et al. Sputum and BAL Clara cell secretory protein and surfactant protein D levels in asthma. *Allergy*. 2015;70(6):711-714.
53. Ma YN, Wang J, Lee YL, et al. Association of urine CC16 and lung function and asthma in Chinese children. *Allergy Asthma Proc*. 2015;36(4):59-64.
54. Chen LC, Tseng HM, Wu CJ, et al. Evaluation of a common variant of the gene encoding clara cell 10 kd protein (CC10) as a candidate determinant for asthma severity and steroid responsiveness among Chinese children. *J Asthma*. 2012;49(7):665-672.
55. Shijubo N, Itoh Y, Yamaguchi T, et al. Serum levels of Clara cell 10-kDa protein are decreased in patients with asthma. *Lung*. 1999;177(1):45-52.
56. 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(3):930-933.

57. Roth FD, Quintar AA, Uribe Echevarria EM, Torres AI, Aoki A, Maldonado CA. Budesonide effects on Clara cell under normal and allergic inflammatory condition. *Histochem Cell Biol*. 2007;127(1):55-68.
58. An JY, Ahn C, Kang HY, Jeung EB. Inhibition of mucin secretion via glucocorticoid-induced regulation of calcium-related proteins in mouse lung. *Am J Physiol Lung Cell Mol Physiol*. 2018;314(6):L956-L966.
59. de Burbure C, Pignatti P, Corradi M, et al. Uteroglobin-related protein 1 and Clara cell protein in induced sputum of patients with asthma and rhinitis. *Chest*. 2007;131(1):172-179.
60. Laucho-Contreras ME, Polverino F, Gupta K, et al. Protective role for club cell secretory protein-16 (CC16) in the development of COPD. *Eur Respir J*. 2015;45(6):1544-1556.
61. Zhu L, Di PY, Wu R, Pinkerton KE, Chen Y. Repression of CC16 by cigarette smoke (CS) exposure. *PLoS One*. 2015;10(1):e0116159.
62. 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(12):1413-1419.
63. Milne S, Li X, Hernandez Cordero AI, et al. Protective effect of club cell secretory protein (CC-16) on COPD risk and progression: a Mendelian randomisation study. *Thorax*. 2020;75(11):934-943.
64. Wolfson MR, Funanage VL, Kirwin SM, et al. Recombinant human Clara cell secretory protein treatment increases lung mRNA expression of surfactant proteins and vascular endothelial growth factor in a premature lamb model of respiratory distress syndrome. *Am J Perinatol*. 2008;25(10):637-645.
65. Laguna TA, Williams CB, Brandy KR, et al. Sputum club cell protein concentration is associated with pulmonary exacerbation in cystic fibrosis. *J Cyst Fibros*. 2015;14(3):334-340.
66. Starosta V, Ratjen F, Rietschel E, Paul K, Griese M. Anti-inflammatory cytokines in cystic fibrosis lung disease. *Eur Respir J*. 2006;28(3):581-587.
67. Snyder JC, Reynolds SD, Hollingsworth JW, Li Z, Kaminski N, Stripp BR. Clara cells attenuate the inflammatory response through regulation of macrophage behavior. *Am J Respir Cell Mol Biol*. 2010;42(2):161-171.
68. Ogilvie V, Passmore M, Hyndman L, et al. Differential global gene expression in cystic fibrosis nasal and bronchial epithelium. *Genomics*. 2011;98(5):327-336.
69. Baumann R, Untersmayr E, Zissler UM, et al. Non-invasive and minimally-invasive techniques for the diagnosis and management of allergic diseases. *Allergy*. 2021;76(4):1010–1023. https://doi.org/10.1111/all.14645
70. Guerra S, Halonen M, Vasquez MM, et al. Relation between circulating CC16 concentrations, lung function, and development of chronic obstructive pulmonary disease across the lifespan: a prospective study. *Lancet Respir Med*. 2015;3(8):613-620.
71. Lin J, Zhang W, Wang L, Tian F. Diagnostic and prognostic values of Club cell protein 16 (CC16) in critical care patients with acute respiratory distress syndrome. *J Clin Lab Anal*. 2018;32(2):e22262.
72. Wendt C, Tram K, Price A, England K, Stiehm A, Panoskaltsis-Mortari A. Club cell secretory protein improves survival in a murine obliterative bronchiolitis model. *Am J Physiol Lung Cell Mol Physiol*. 2013;305(9):L642-650.
73. Miller TL, Shashikant BN, Melby JM, Pilon AL, Shaffer TH, Wolfson MR. Recombinant human Clara cell secretory protein in acute lung injury of the rabbit: effect of route of administration. *Pediatr Crit Care Med*. 2005;6(6):698-706.
74. Mukherjee AB, Zhang Z, Chilton BS. Uteroglobin: a steroid-inducible immunomodulatory protein that founded the Secretoglobin superfamily. *Endocr Rev*. 2007;28(7):707-725.
75. Gamez AS, Gras D, Petit A, et al. Supplementing defect in club cell secretory protein attenuates airway inflammation in COPD. *Chest*. 2015;147(6):1467-1476.
76. Laguna TA, Williams CB, Nunez MG, et al. Biomarkers of inflammation in infants with cystic fibrosis. *Respir Res*. 2018;19(1):6.
77. Vasanthakumar G, Manjunath R, Mukherjee AB, Warabi H, Schiffmann E. Inhibition of phagocyte chemotaxis by uteroglobin, an inhibitor of blastocyst rejection. *Biochem Pharmacol*. 1988;37(3):389-394.
78. Ray R, Zhang Z, Lee YC, Gao JL, Mukherjee AB. Uteroglobin suppresses allergen-induced TH2 differentiation by down-regulating the expression of serum amyloid A and SOCS-3 genes. *FEBS Lett*. 2006;580(25):6022-6026.
79. Xu B, Janicova A, Vollrath JT, et al. Club cell protein 16 in sera from trauma patients modulates neutrophil migration and functionality via CXCR1 and CXCR2. *Mol Med*. 2019;25(1):45.
80. Liu Y, Yu HJ, Wang N, et al. Clara cell 10-kDa protein inhibits T(H)17 responses through modulating dendritic cells in the setting of allergic rhinitis. *J Allergy Clin Immunol*. 2013;131(2):387-394.e12.
81. Xu M, Yang W, Wang X, Nayak DK. Lung Secretoglobin Scgb1a1 influences alveolar macrophage-mediated inflammation and immunity. *Front Immunol*. 2020;11:584310.
82. Arsalane K, Broeckaert F, Knoops B, Wiedig M, Toubeau G, Bernard A. Clara cell specific protein (CC16) expression after acute lung inflammation induced by intratracheal lipopolysaccharide administration. *Am J Respir Crit Care Med*. 2000;161(5):1624-1630.
83. Michel O, Murdoch R, Bernard A. Inhaled LPS induces blood release of Clara cell specific protein (CC16) in human beings. *J Allergy Clin Immunol*. 2005;115(6):1143-1147.
84. Yao XL, Levine SJ, Cowan MJ, Logun C, Shelhamer JH. Tumor necrosis factor-alpha stimulates human Clara cell secretory protein production by human airway epithelial cells. *Am J Respir Cell Mol Biol*. 1998;19(4):629-635.
85. Zheng F, Kundu GC, Zhang Z, Ward J, DeMayo F, Mukherjee AB. Uteroglobin is essential in preventing immunoglobulin A nephropathy in mice. *Nat Med*. 1999;5(9):1018-1025.
86. Zhang Z, Kundu GC, Yuan CJ, et al. Severe fibronectin-deposit renal glomerular disease in mice lacking uteroglobin. *Science*. 1997;276(5317):1408-1412.
87. Hynes RO. Fibronectins: a family of complex and versatile adhesive glycoproteins derived from a single gene. *Harvey Lect*. 1985–1986;81:133-152.
88. Wang X, Tanino Y, Sato S, et al. Secretoglobin 3A2 attenuates lipopolysaccharide-induced inflammation through inhibition of ERK and JNK pathways in bronchial epithelial cells. *Inflammation*. 2015;38(2):828-834.
89. Choi MS, Ray R, Zhang Z, Mukherjee AB. IFN-gamma stimulates the expression of a novel secretoglobin that regulates chemotactic cell migration and invasion. *J Immunol*. 2004;172(7):4245-4252.
90. Dierynck I, Bernard A, Roels H, De Ley M. Potent inhibition of both human interferon-gamma production and biologic activity by the Clara cell protein CC16. *Am J Respir Cell Mol Biol*. 1995;12(2):205-210.
91. Yamada A, Suzuki D, Miyazono A, et al. IFN-gamma down-regulates Secretoglobin 3A1 gene expression. *Biochem Biophys Res Commun*. 2009;379(4):964-968.
92. Ramsay PL, Luo Z, Magdaleno SM, et al. Transcriptional regulation of CCSP by interferon-gamma in vitro and in vivo. *Am J Physiol Lung Cell Mol Physiol*. 2003;284(1):L108-118.
93. Liu Y, Lu X, Yu HJ, et al. The expression of osteopontin and its association with Clara cell 10 kDa protein in allergic rhinitis. *Clin Exp Allergy*. 2010;40(11):1632-1641.
94. Xanthou G, Alissafi T, Semitekolou M, et al. Osteopontin has a crucial role in allergic airway disease through regulation of dendritic cell subsets. *Nat Med*. 2007;13(5):570-578.
95. Kido T, Tomita T, Okamoto M, et al. FOXA1 plays a role in regulating secretoglobin 1a1 expression in the absence of CCAAT/enhancer binding protein activities in lung in vivo. *Am J Physiol Lung Cell Mol Physiol*. 2011;300(3):L441-452.
96. Minoo P, Hu L, Xing Y, et al. Physical and functional interactions between homeodomain NKX2.1 and winged helix/forkhead FOXA1 in lung epithelial cells. *Mol Cell Biol*. 2007;27(6):2155-2165.

97. Sawaya PL, Luse DS. Two members of the HNF-3 family have opposite effects on a lung transcriptional element; HNF-3 alpha stimulates and HNF-3 beta inhibits activity of region I from the Clara cell secretory protein (CCSP) promoter. *J Biol Chem*. 1994;269(35):22211-22216.
98. Sawaya PL, Stripp BR, Whitsett JA, Luse DS. The lung-specific CC10 gene is regulated by transcription factors from the AP-1, octamer, and hepatocyte nuclear factor 3 families. *Mol Cell Biol*. 1993;13(7):3860-3871.
99. Seki Y, Inoue H, Nagata N, et al. SOCS-3 regulates onset and maintenance of T(H)2-mediated allergic responses. *Nat Med*. 2003;9(8):1047-1054.
100. Yoshikawa S, Miyahara T, Reynolds SD, et al. Clara cell secretory protein and phospholipase A2 activity modulate acute ventilator-induced lung injury in mice. *J Appl Physiol (1985)*. 2005;98(4):1264-1271.
101. Sokolowska M, Rovati GE, Diamant Z, et al. Current perspective on eicosanoids in asthma and allergic diseases: EAACI Task Force consensus report, part I. *Allergy*. 2021;76(1):114-130.
102. Niewoehner DE, Rice K, Duane P, Sinha AA, Gebhard R, Wangensteen D. Induction of alveolar epithelial injury by phospholipase A2. *J Appl Physiol (1985)*. 1989;66(1):261-267.
103. Nagase T, Uozumi N, Ishii S, et al. Acute lung injury by sepsis and acid aspiration: a key role for cytosolic phospholipase A2. *Nat Immunol*. 2000;1(1):42-46.
104. Mandal AK, Zhang Z, Ray R, et al. Uteroglobin represses allergen-induced inflammatory response by blocking PGD2 receptor-mediated functions. *J Exp Med*. 2004;199(10):1317-1330.
105. Yoneda M, Xu L, Kajiyama H, et al. Secretoglobin superfamily protein SCGB3A2 alleviates house dust mite-induced allergic airway inflammation in mice. *Int Arch Allergy Immunol*. 2016;171(1):36-44.
106. Chiba Y, Srisodsai A, Supavilai P, Kimura S. Interleukin-5 reduces the expression of uteroglobin-related protein (UGRP) 1 gene in allergic airway inflammation. *Immunol Lett*. 2005;97(1):123-129.
107. Yamada A, Kimura S. Induction of uteroglobin-related protein 2 (Ugrp2) expression by EGF and TGFalpha. *FEBS Lett*. 2005;579(10):2221-2225.
108. Umland TC, Swaminathan S, Furey W, Singh G, Pletcher J, Sax M. Refined structure of rat Clara cell 17 kDa protein at 3.0 A resolution. *J Mol Biol*. 1992;224(2):441-448.
109. Weeraratna AT, Cajigas JA, Schwartz A, Enquist EG, Manyak MJ, Patierno SR. Loss of uteroglobin expression in prostate cancer: relationship to advancing grade. *Clin Cancer Res*. 1997;3(12 Pt 1):2295-2300.
110. Linnoila RI, Szabo E, DeMayo F, Witschi H, Sabourin C, Malkinson A. The role of CC10 in pulmonary carcinogenesis: from a marker to tumor suppression. *Ann N Y Acad Sci*. 2000;923:249-267.
111. Sjodin A, Guo D, Sorhaug S, Bjermer L, Henriksson R, Hedman H. Dysregulated secretoglobin expression in human lung cancers. *Lung Cancer*. 2003;41(1):49-56.
112. Zafrakas M, Petschke B, Donner A, et al. Expression analysis of mammaglobin A (SCGB2A2) and lipophilin B (SCGB1D2) in more than 300 human tumors and matching normal tissues reveals their co-expression in gynecologic malignancies. *BMC Cancer*. 2006;6:88.
113. Hassan EM, Willmore WG, McKay BC, DeRosa MC. In vitro selections of mammaglobin A and mammaglobin B aptamers for the recognition of circulating breast tumor cells. *Sci Rep*. 2017;7(1):14487.
114. Ouellette RJ, Richard D, Maicas E. RT-PCR for mammaglobin genes, MGB1 and MGB2, identifies breast cancer micrometastases in sentinel lymph nodes. *Am J Clin Pathol*. 2004;121(5):637-643.
115. Tassi RA, Bignotti E, Rossi E, et al. Overexpression of mammaglobin B in epithelial ovarian carcinomas. *Gynecol Oncol*. 2007;105(3):578-585.
116. Tassi RA, Calza S, Ravaggi A, et al. Mammaglobin B is an independent prognostic marker in epithelial ovarian cancer and its expression is associated with reduced risk of disease recurrence. *BMC Cancer*. 2009;9:253.
117. Munakata K, Uemura M, Takemasa I, et al. SCGB2A1 is a novel prognostic marker for colorectal cancer associated with chemoresistance and radioresistance. *Int J Oncol*. 2014;44(5):1521-1528.
118. Zhou H, Zou X, Li H, Li T, Chen L, Cheng X. Decreased secretoglobin family 2A member 1expression is associated with poor outcomes in endometrial cancer. *Oncol Lett*. 2020;20(4):24.
119. Tassi RA, Bignotti E, Falchetti M, et al. Mammaglobin B expression in human endometrial cancer. *Int J Gynecol Cancer*. 2008;18(5):1090-1096.
120. Aihara T, Fujiwara Y, Miyake Y, et al. Mammaglobin B gene as a novel marker for lymph node micrometastasis in patients with abdominal cancers. *Cancer Lett*. 2000;150(1):79-84.
121. Wu X, Xiao Y, Zhou Y, Zhou Z, Yan W. lncRNA SNHG20 promotes prostate cancer migration and invasion via targeting the miR-6516-5p/SCGB2A1 axis. *Am J Transl Res*. 2019;11(8):5162-5169.
122. Wong RL, Wang Q, Trevino LS, et al. Identification of secretaglobin Scgb2a1 as a target for developmental reprogramming by BPA in the rat prostate. *Epigenetics*. 2015;10(2):127-134.
123. Li J, Xu W, Zhu Y. Mammaglobin B may be a prognostic biomarker of uterine corpus endometrial cancer. *Oncol Lett*. 2020;20(5):255.
124. Talaat IM, Hachim MY, Hachim IY, Ibrahim RAE, Ahmed M, Tayel HY. Bone marrow mammaglobin-1 (SCGB2A2) immunohistochemistry expression as a breast cancer specific marker for early detection of bone marrow micrometastases. *Sci Rep*. 2020;10(1):13061.
125. Kurotani R, Shima R, Miyano Y, et al. SCGB3A2 inhibits acrolein-induced apoptosis through decreased p53 phosphorylation. *Acta Histochem Cytochem*. 2015;48(2):61-68.
126. Yokoyama S, Nakayama S, Xu L, Pilon AL, Kimura S. Secretoglobin 3A2 eliminates human cancer cells through pyroptosis. *Cell Death Discov*. 2021;7(1):12.
127. Kurotani R, Kumaki N, Naizhen X, Ward JM, Linnoila RI, Kimura S. Secretoglobin 3A2/uteroglobin-related protein 1 is a novel marker for pulmonary carcinoma in mice and humans. *Lung Cancer*. 2011;71(1):42-48.
128. Chiba Y, Kurotani R, Kusakabe T, et al. Uteroglobin-related protein 1 expression suppresses allergic airway inflammation in mice. *Am J Respir Crit Care Med*. 2006;173(9):958-964.
129. Srisodsai A, Kurotani R, Chiba Y, et al. Interleukin-10 induces uteroglobin-related protein (UGRP) 1 gene expression in lung epithelial cells through homeodomain transcription factor T/EBP/NKX2.1. *J Biol Chem*. 2004;279(52):54358-54368.
130. www.genecards.org.
131. Porter D, Lahti-Domenici J, Torres-Arzayus M, Chin L, Polyak K. Expression of high in normal-1 (HIN-1) and uteroglobin related protein-1 (UGRP-1) in adult and developing tissues. *Mech Dev*. 2002;114(1–2):201-204.
132. Stoeckelhuber M, Messmer EM, Schmidt C, Xiao F, Schubert C, Klug J. Immunohistochemical analysis of secretoglobin SCGB 2A1 expression in human ocular glands and tissues. *Histochem Cell Biol*. 2006;126(1):103-109.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Mootz M, Jakwerth CA, Schmidt-Weber CB, Zissler UM. Secretoglobins in the big picture of immunoregulation in airway diseases. *Allergy*. 2021;00:1–11. https://doi.org/10.1111/all.15033