

🔗 An Elusive Fox that Suppresses *Scgb1a1* in Asthma Has Been Found

Asthma is a worldwide chronic airways disease that affects more than 300 million children and adults worldwide (1). Affected individuals suffer from wheezing, chest tightness, shortness of breath, and cough that is attributed to airway narrowing, excessive mucus production, and persistent inflammation. Symptoms often begin in early childhood and are believed to be initiated by a severe inflammatory response in a developmentally immature immune system. Initiating factors include infection with rhinovirus or other respiratory viral infections, exposure to particulate matter such as tobacco smoke or air pollution, and even supplemental oxygen used to treat preterm infants. Asthma exacerbations typically occur after exercise, T-helper cell type 2 (Th2)-mediated allergic responses, respiratory infections, and exposure to various pulmonary irritants. Although it is a minor inconvenience for most individuals, asthma can be a major, life-threatening health concern for others. The key to understanding this variability lies in defining the complex gene–environment interactions that drive asthma and other airway diseases such as chronic obstructive pulmonary disease (COPD). In this issue of the *Journal*, Zhu and colleagues (pp. 695–704), report on what may be a key observation in furthering our understanding of why the airway epithelium of individuals with asthma or COPD have less secretoglobin family 1A member 1 (SCGB1A1; also known as club cell secretory protein [CCSP], CC10, and CC16) compared with healthy control subjects (2). In their studies, they discovered that viral infections and Th2 cytokines inhibit expression of SCGB1A1 by inhibiting expression of the transcription factor forkhead box A2 (FOXA2), which is known to regulate Th2-mediated inflammation and goblet cell hyperplasia.

So why is this important? SCGB1A1 is a small homodimeric molecule that is secreted by nonciliated airway club cells and mucous-producing cells of the uterus. It is the most abundant protein found in airway lining fluid, and can be detected in serum and urine. Although its exact physiologic function has yet to be defined, SCGB1A1 possesses antiinflammatory and antitoxicant properties via its ability to inhibit phospholipase A2 activity, sequester hydrophobic ligands such as polychlorinated biphenyls and steroids, alter chemotaxis, and affect cytokine production (3). These properties indicate that SCGB1A1 is an important defense molecule of the lung. Hence, it is not surprising that lower levels of SCGB1A1 have been detected in BAL fluid, serum, and urine of individuals with asthma or and COPD compared with healthy control subjects (4). Similarly, airspace enlargement is greater in *Scgb1a1-null* mice exposed to cigarette smoke than wild-type controls. Additionally, several inflammatory and autoimmune diseases have been associated with a SNP in the *Scgb1a1* gene, resulting in reduced levels of SCGB1A1 protein (5). Improving the respiratory health of individuals with asthma or COPD therefore requires a better understanding of how SCGB1A1 is suppressed.

To identify factors capable of suppressing SCGB1A1 in airways disease, Zhu and colleagues analyzed three previously published transcriptomic datasets of human brushed bronchial epithelial cells isolated from subjects with asthma and control subjects without asthma. They confirmed that individuals with asthma express less *Scgb1a1* mRNA than those without asthma, and found that this correlated with reduced mRNA encoding FOXA2, a known transcriptional inducer of *Scgb1a1* mRNA. The authors went on to show that 1) *Scgb1a1* and *FoxA2* were both suppressed in an ovalbumin mouse model of airway hyperreactivity, 2) the Th2 cytokines IL-4 and IL-13 suppressed epithelial expression of both FOXA2 and SCGB1A1, 3) rhinovirus infection inhibited epithelial expression of these two proteins, and 4) overexpression of FOXA2 stimulated *Scgb1a1* transcription and abundance of SCGB1A1 protein. Perhaps most compelling is the observation that overexpression of FOXA2 restored expression of SCGB1A1 in epithelial cells treated with IL-13 or infected with rhinovirus. Collectively, these findings provide strong experimental evidence that two known mediators of airways disease, namely, rhinovirus and Th2 cytokines, can suppress epithelial expression of SCGB1A1 via inhibition of FOXA2 (Figure 1). Such knowledge may prove to be a critical key needed to restore expression of SCGB1A1 in the airways of individuals with asthma or COPD.

This discovery also raises new questions and opportunities for further research. The current study used *Scgb1a1-null* mice to show how complete loss of SCGB1A1 potentiated airway hyperreactivity and responsiveness to ovalbumin challenge. It remains to be determined how loss of SCGB1A1 affects airway function. A recent paper showing that *Scgb1a1-null* mice have higher levels of collagen and ACTA2 in their lungs than wild-type mice suggests that SCGB1A1 influences airway structure (6). An emerging concept is that individuals with asthma may have leaky airways that permit the transepithelial passage of inhaled allergens and other proinflammatory pollutants into the underlying interstitial space (7). Loss of SCGB1A1 may therefore reflect a change in the airway club cell phenotype and consequently a change in airway barrier integrity. Another study found a slow but steady loss of *Scgb1a1* in irradiated mice infected with influenza A virus (8). Loss of SCGB1A1 was attributed to loss of club cells, perhaps because distal airway progenitor cells are radiosensitive (9). The slow loss of SCGB1A1 after radiation may be useful for defining a threshold of SCGB1A1 that correlates with increased airway hyperreactivity. It is also important to note that protein abundance does not always equate with functional activity. For example, increased oxidation of SCGB1A1 has been observed in tracheal aspirates of preterm infants who went on to develop bronchopulmonary dysplasia (10). Whether oxidation of SCGB1A1 impairs function and contributes

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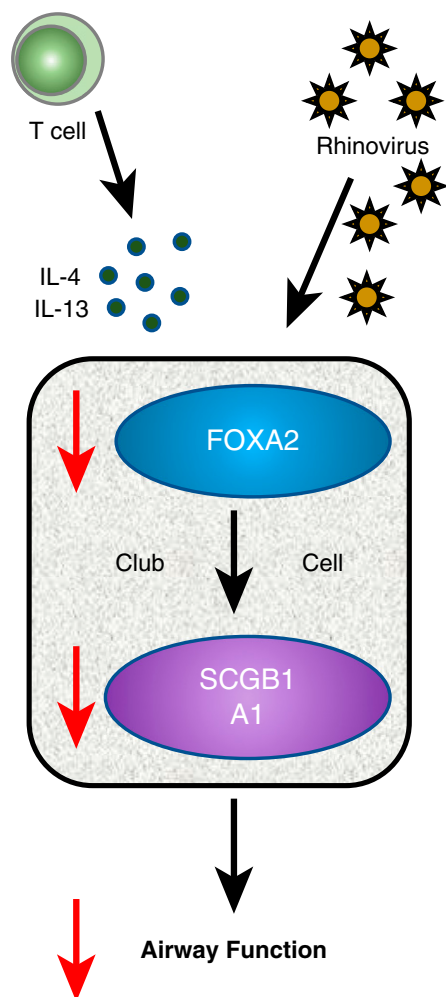


Figure 1. Cartoon model summarizing the key findings of Zhu and colleagues (2). The production of T-helper cell type 2 cytokines such as IL-4 and IL-13 or infection with rhinovirus suppresses expression of FOXA2 in club cells. The loss of FOXA2 leads to loss of SCGB1A1 and the loss of proper airway function, such as that seen in asthma and chronic obstructive pulmonary disease. Red arrows reflect loss in protein expression and reduced airway function. FOXA2 = forkhead box A2; SCGB1 = secretoglobulin family 1A member 1.

to the enhanced incidence of airway wheezing reported in preterm-born infants remains to be determined. Regardless, these types of studies suggest that loss of SCGB1A1 expression or activity can cause airways disease through multiple mechanisms that remain to be fully understood.

The study by Zhu and colleagues also raises the question of persistence. Specifically, why are SCGB1A1 and FOXA2 persistently suppressed even when the initial inflammatory response or infection has subsided? It is known that genetic deletion of FoxA2 in the developing respiratory epithelium promotes an asthmatic phenotype reflected by increased recruitment and activation of myeloid dendritic cells, increased transcription of Alox15 and production of leukotrienes, and consequently goblet cell hyperplasia (11–13). This dramatic reprogramming of the airway epithelium suggests that FOXA2

might drive other types of airways disease. Indeed, in a previous study, frequent suppression of FOXA2 was observed in lung cancer cell lines and non-small cell lung carcinomas (14). Intriguingly, in that study, loss of FOXA2 expression in lung cancer was attributed to hypermethylation of the FoxA2 promoter. It would not be surprising to find that allergens and other environmental exposures may drive asthma via epigenetic changes that drive persistent suppression of FoxA2 transcription.

In summary, the paper by Zhu and colleagues is important because it provides compelling evidence that Th2 cytokines and viral infections may drive asthma via epithelial loss of FOXA2 and consequently loss of SCGB1A1. We should remember that FOXA2 is one of 44 members in the forkhead family of transcription factors (15) and that these proteins play important roles in regulating the expression of genes involved in cell proliferation, differentiation, and longevity. A closer look in the lung may reveal other elusive Foxes that adversely affect pulmonary function and respiratory health. ■

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Rachel Warren, M.S.
Michael A. O'Reilly, Ph.D.
School of Medicine and Dentistry
University of Rochester
Rochester, New York

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