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# Pendrin Function in Airway Epithelia

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**Key Words**

Interleukin • Cytokine • SLC26A4 • Chronic obstructive pulmonary disease • Mucus • Pendred syndrome • Sensorineural hearing loss • Asthma

**Abstract**

The expression and function of the anion exchanger pendrin (SLC26A4) was thought to be limited mainly to the inner ear, kidney and thyroid. Recent data indicates that pendrin is also expressed in the bronchial epithelium following exposure to the $T_H2$-type cytokines, interleukin (IL)-4 and IL-13. Expression of the transporter is also upregulated in bronchial asthma and chronic obstructive pulmonary disease. Both diseases involve respiratory inflammation leading to tissue destruction/remodeling and decreased airway function, and data so far indicate that increased pendrin expression and/or activity might contribute to their pathogenesis. In this review, we summarize data that have emerged within the past years aimed at revealing the role for pendrin in the airway epithelia.



## Introduction

Pendrin (SLC26A4) is an integral membrane protein exchanging anions like bicarbonate, iodide and others for chloride [1]. The protein is predominantly expressed in the inner ear, thyroid gland, and the kidney [2-5]. Expression has also been documented in other organs, including the airway epithelia [6-11], mammary gland [12], testis [5], placenta [13], endometrium [14] and liver [15], albeit much lower with respect to those mentioned earlier. Mutations impairing pendrin function are manifested as Pendred Syndrome (PS), an autosomal recessive disorder characterized by prelingual deafness and an iodide organification defect that may or may not be accompanied with goiter [16-19]. Within the past years, increased pendrin expression has been linked to respiratory diseases including bronchial asthma, chronic obstructive pulmonary disease (COPD) and rhinovirus infection [6-9, 20, 21]. While asthma and COPD both compromise lung function, they are distinct entities. Asthma is a reversible respiratory condition in which bronchial spasms result in breathing difficulty, and is usually caused by an allergic reaction or some other form of

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hypersensitivity. COPD, on the other hand, is an irreversible, long-term obstruction of lung airflow interfering with normal breathing. While it is becoming more and more evident that pendrin is associated with these respiratory diseases, the actual role that the anion transporter plays in the respiratory epithelium is unclear.

## Asthma and COPD

In 2004, the World Health Organization (WHO) estimated that worldwide, 64 million people have COPD and 235 million have asthma. COPD was the fourth leading cause of death in 2004 [22], and the disease is expected to rise to the third leading cause of death by the year 2030 [23]. While asthma does not compare with COPD in terms of mortality (only 3,447 asthma-induced deaths in 2007 in the USA [24]), the social and economic costs of asthma are estimated to be an astounding 18 billion USD per year [25]. Interestingly, asthma has been identified as a risk factor for COPD development [26].

Both diseases involve respiratory inflammation leading to tissue destruction/remodeling and decreased airway function [27-30]. The immunopathogenesis of each disease is largely distinct, but some overlap is apparent. COPD predominantly involves neutrophil, macrophage and CD8+ T-cell activation, and the resulting inflammation is mediated mainly by $T_H1$-type cytokines (leukotriene B4 (LTB4), IL-1, IL-8 and **t**umor **n**ecrosis **f**actor (TNF)$\alpha$, for example). On the other hand, asthma pathogenesis primarily involves activation of eosinophils and CD4+ T-cells, with downstream inflammation mediated mainly by $T_H2$-type cytokines (IL-3, IL-4, IL-5, IL-9, IL-13, and **g**ranulocyte **m**acrophage **c**olony **s**timulating **f**actor (GM-CSF) for instance). Respiratory symptoms common to asthma and COPD include subepithelial fibrosis and mucus metaplasia/hypersecretion (a major factor responsible for morbidity and mortality in the aforementioned diseases [31]), both of which can result from $T_H1$-type and $T_H2$-type cytokine signaling [27, 32].

## IL-4 and IL-13 Signal Transduction

Recently, increased pendrin expression has been demonstrated in bronchial epithelial cells following exposure to IL-4 and IL-13 [6-11]. These cytokines are small glycoproteins produced and secreted by various leukocytes and play important roles in the immune system and intercellular communication. IL-13 is considered a central mediator of allergic asthma, since it induces **a**irway **h**yper-**r**esponsiveness (AHR), acute eosinophilia, and IgE and mucus production [33]. One of the main downstream effects of IL-4 and IL-13 signaling is activation of the **s**ignal **t**ransducer and **a**ctivator of **t**ranscription (STAT) 6 protein (also known as IL-4 **n**uclear **a**ctivated **f**actor, IL-4NAF). Following ligand-receptor binding, associated **Ja**nus **k**inases (JAKs) activate the receptor, allowing STAT6 to then be recruited and activated (by phosphorylation). Once phosphorylated, STAT6 homodimerizes and translocates to the nucleus where it regulates the transcription of target genes. The expression of STAT6 is upregulated in the bronchial epithelium of asthma patients [34] and the levels of both IL-4 and IL-13 are increased in the serum of human asthmatic patients [35-39], as well as in the **b**roncho**a**lveolar **l**avage (BAL) fluid and serum of allergen-sensitized rats [40].

## IL-4 and IL-13 and Airway Epithelial Ion Channels and Transporters

IL-4 and IL-13 have been reported to modulate the expression of a variety of ion channels and transporters, as well as **aq**ua**p**orins (AQPs) within the respiratory epithelium. Even more complex is that the cytokines can differently effect the direction of ion fluxes through these entities depending on the cell type. For example, IL-4 conferred a reabsorptive phenotype to T84 colonic cells by decreasing both forskolin and carbachol -stimulated $Cl^-$ secretion and fluid transport [41], whereas the same cytokine induced a secretory phenotype in **h**uman **b**ronchial **e**pithelial (HBE) cells by decreasing amiloride-sensitive **s**hort-**c**ircuit **c**urrent ($I_{SC}$) and enhancing forskolin and UTP-stimulated $I_{SC}$ [42]. Amiloride-sensitive $I_{SC}$ is indicative of $Na^+$ transport via the **e**pithelial **s**odium **c**hannel (ENaC), while forskolin, carbachol and UTP can induce activation and subsequent chloride transport through the **c**ystic **f**ibrosis **t**ransmembrane **r**egulator (CFTR) and $Ca^{2+}$-activated chloride channels (CaCCs, CLCA), respectively. Changes in ion transport through these channels can occur by alterations in number and/or

expression levels of active channels, open probability and/or single channel conductance. In bronchial epithelial cells, IL-4 has been shown to alter ion transport by changes in expression; the cytokine decreased expression of the β and γ subunits of ENaC [43], and increased the expression of CFTR [43], CLCA1 and CLCA3 (human equivalent of murine gob-5) [6, 44, 45].While the end effect on ion transport (in terms of direction) by IL-4 and IL-13 seems to be tissue-dependent, a common theme emerges; both cytokines alter $Na^+$ and $Cl^-$ current. In terms of AQP regulation, both the mRNA and protein levels of two AQP isoforms are regulated by IL-13 in the lung; AQP3 is increased whereas AQP5 is decreased [46]. Interestingly, decreased expression of this water channel isoform has been associated with increased mucus production [47, 48].

## Pendrin and the Airways

The link between airway disease and pendrin was demonstrated first in 2005, in which pendrin message was upregulated in three different murine asthma models; two of which included transgenic overexpression of IL-13 in the lung [7]. Pendrin mRNA was increased 23-fold in primary HBE cultures treated with IL-4 [11]. In the same study, IL-4 increased the electroneutral, pendrin-mediated exchange of thiocyanate ($SCN^-$) and $Cl^-$, as well as the unilateral transport of $SCN^-$ by CFTR and CaCCs. Recently, Garnett et al. showed that pendrin plays a critical role in transcellular $HCO_3^-$ secretion in Calu-3 airway serous cells [49].

We showed that IL-13 increased the mRNA expression of pendrin, Clca3 and mucin 5, subtypes A and C (Muc5ac, a major glycoprotein component of mucus) in lung tissue of normal, BALB/c mice [9]. In the same study, asthma and COPD were simulated in mice by inhalation of either ovalbumin (OVA) or porcine pancrease elastase (PPE), respectively. Both simulations resulted in increased pendrin mRNA and protein expression, as well as an increase in the presence of mucins (as assessed by H&E and PAS/Alcian staining). Asthma simulation also increased the mRNA levels of Clca3 while COPD simulation increased the expression of Muc5ac mRNA. The most striking results included those induced soley by the overexpression of pendrin. In mice, the enforced overexpression of pendrin in lung tissue resulted in increases in i) AHR, ii) formation of mucus exudates, iii) neutrophilic infiltration and iv) expression of Muc5ac protein in the BAL fluid. In a separate study, OVA-stimulated pendrin knock-out mice displayed less AHR, eosinophilia and inflammation than their wild-type counterparts [8]. These data, albeit from mouse models, suggest that pendrin might be a common denominator in asthma and COPD.

The IL-13-mediated increases in the expression of pendrin, ClCa3 and Muc5ac mRNA that we showed were not evident in STAT6 knockout mice [9]. This observation, along with the data linking IL-4 to increased pendrin expression, prompted an in-depth investigation of the mechanism of IL-4 and IL-13 stimulated increases in pendrin expression. As previously mentioned, IL-4 and IL-13 signaling involves activation of STAT6. The transcription factor prefers to bind with $N_4$ interferon-γ **a**ctivated **s**equence (GAS) motifs (5' TTC($N_4$)GAA 3', where N is any nucleotide) in the promoter regions of target genes [50]. The pendrin promoter contains at least one $N_4$ GAS motif, and we showed that STAT6 bound this sequence *in vitro*. Moreover, both IL-4 and IL-13 increased the promoter activity of pendrin, an effect that required an intact $N_4$ GAS motif [10]. We concluded that increases in pendrin promoter activity via STAT6 represent as least one mechanism by which IL-4 and IL-13 increase the message expression of the transporter. Cytokines other than IL-4 and IL-13 may be responsible for increases in pendrin expression. IL-1β, a macrophage secreted cytokine involved in the immunopathogenesis of both asthma and COPD [51], has also been shown to increase pendrin mRNA levels in human bronchial epithelial cells [11].

The importance of proper homeostatic maintenance of the thickness and composition of the **a**irway **s**urface **l**iquid (ASL) by the underlying respiratory epithelium is underscored by the expression of multiple ion channel transporter entities, AQP water channels, salt-sensitive enzymes and peptide antibiotics. Pedemonte et al. showed that pendrin-mediated $SCN^-$ transport into the ASL is involved in the production of the antimicrobial molecule hypothiocyanite ($OSCN^-$) [11]. In this context, $SCN^-$ is oxidized into $OSCN^-$ in the presence of hydrogen peroxide ($H_2O_2$), generated by **du**al NADPH **ox**idases DUOX1 and DUOX2, and **l**acto**p**er**o**xidase (LPO) (Fig. 1). Like pendrin, the expression of DUOX1 is upregulated by IL-4 and IL-13 in airway epithelial

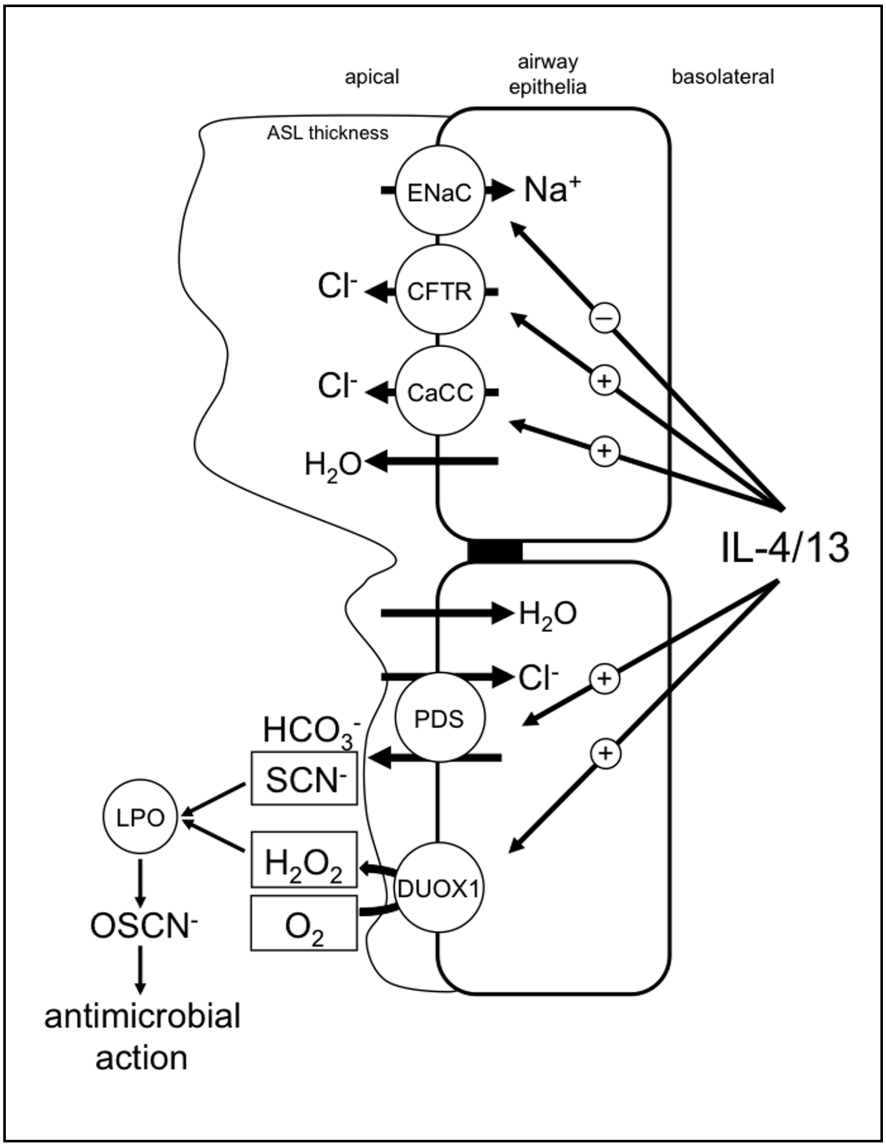


**Fig. 1.** Regulation of airway surface liquid (ASL) thickness by IL-4 and IL-13, and roles of pendrin in bronchial epithelial cells. In bronchial epithelial cells, IL-4 and IL-13 induce a secretory phenotype by stimulating chloride ($Cl^-$) secretion via CFTR and calcium ($Ca^{2+}$)-activated chloride channels (CaCCs), and by decreasing sodium ($Na^+$) reabsorption via ENaC. This leads to increased water secretion and ASL thickness. Both cytokines also increase the expression and function of pendrin (PDS), resulting in the reabsorption of water and decreased ASL thickness. Pendrin can also increase thiocyanite ($SCN^-$) secretion, which, in the presence of hydrogen peroxide ($H_2O_2$) generated by DUOX1, can contribute to the production of the antimicrobial agent hypothiocyanite ($OSCN^-$) by the lactoperoxidase (LPO) system. The contribution of aquaporins to ASL thickness is not shown in this cartoon; nor is the contribution of pendrin to mucus formation.

cells [11, 52, 53]. Therefore, pendrin and DUOX1/2 overexpression may act in counteracting microbial infection.

## Pendrin as a Therapeutic Target in Asthma and COPD

The mainstream therapies for asthma and COPD are largely different, but have some commonalities. Corticosteroids as anti-inflammatory agents and short- and long-acting β-adrenergic agonists as bronchodilators are popular asthma therapies, whereas anti-cholinergics as bronchodilators are predominantly used in COPD. Corticosteroid use in COPD exists, but is less compared with asthma. Despite the relatively high effectiveness of these therapies, disease control in certain patient populations (severe asthma, for example) remains unmet, partly due to low patient compliance. In recent years, blockade of cytokine signaling (antibodies as ligand and receptor blockers, soluble forms of dominant negative ligand, and inhibitors of intermediate signaling proteins) as a means of counteracting inflammation has been a focus in regards to drug development. At least for asthma, specific inhibition of $T_H2$-type cytokine signaling has predominated. The majority of anti-$T_H2$-type cytokine signaling therapies effective in animal models are either ineffective in humans or seem to be patient subtype specific (ie. non-eosinophilic or severe eosinophilic asthma) [28, 54-62]. For example, the anti-IL-13 monoclonal antibody (mAb) lebrikizumab, improved lung function in corticosteroid-

resistant asthmatics, but patients with higher serum levels of periostin had a greater improvement compared to those with lower serum periostin levels [63]. Pitrakinra (AER-001, BAY-16-9996), a soluble, dominant negative form of mutated IL-4, as well as reslizumab and mepoluzimab (IL-5 mAbs) had no overall effect in a group of patients with mild to severe asthma, but did help those patients with severe eosinophilic asthma [56]. AS1517499 [60] and STAT-6-inhibitory peptide (IP) [57] (both STAT6 inhibitors) prevented allergy-induced symptoms in mice, but no information regarding their effects in humans is known.

As already mentioned, inflammation and epithelial barrier remodeling are apparent in both asthma and COPD. It is most often thought that the inflammation leads to remodeling of the airway epithelium, but the converse is also possible [30, 64-66]. As such, it is has been proposed that although inflammation plays a significant role in the pathogenesis of asthma and COPD, significantly more attention should be paid to the impact of airway epithelial remodeling on this process [28, 32, 67].

Pendrin may play a major role in the pathogenesis of asthma or COPD by regulating ASL thickness and mucus production. ENaC, CFTR and CaCCs are regulated by IL-4 and IL-13, and it is clear that at least in lung epithelial cells, reabsorptive $Na^+$ transport through ENaC is suppressed whereas secretory transport of $Cl^-$ through CFTR and CaCCs is stimulated. Together, these actions would result in a net secretory phenotype, resulting in the osmotic flow of water into the lumen and an increase in ASL thickness. Therapies directly targeting sodium reabsorption have presented little, if any value to the problem at hand, since IL-4 and IL-13 (as stated above) already decrease sodium reabsorption in the respiratory epithelium (Fig. 1). It is therefore not surprising that a further decrease in sodium conductance by sodium channel blockers does not dramatically improve the clinical situation. Similarly, preventing overall IL-4/IL-13 signaling, as stated earlier, also seems not to be ideal, since both cytokines result in a net secretory phenotype and increase ASL thickness by inducing the osmotic flow of water into the lumen. However, increased expression of pendrin by IL-4 or IL-13 could promote the exchange of $Cl^-$ into the cell for $HCO_3^-$ into the lumen. Depending on the amount of pendrin activity, the balance of bronchial epithelial ion transport could be tipped towards reabsorption, resulting in the osmotic flow of water into the interstitium and thinning of the ASL. Indeed, the ASL was thicker in IL-13-treated tracheal epithelial cells isolated from pendrin knock out mice compared to wild-type mice (expressing pendrin) [8].

Therefore, it is clear that inflammatory cytokines increase the expression and/or activity of pendrin. What is not clear is when pendrin overexpression occurs in asthma and COPD and if the anion exchanger is involved in epithelial remodeling. Is inflammation a requirement for increased pendrin expression, or does pendrin overexpression occur prior to cytokine release and represent a protein under a cytokine-stimulated positive feedback loop? The best evidence to support this is that overexpression of pendrin *by itself* leads to increases in mucus formation, AHR, and respiratory neutrophilic infiltration [9]. Moreover, pendrin overexpression is common to both asthma and COPD, in which IL-4 and IL-13 signaling has varying contribution to the immunopathogenesis of these diseases. Interestingly, niflumic acid (a non-selective pendrin blocker [68]) dampened the development of IL-13-induced asthma phenotypes in mice [69]. Madeo et al. attempted to make a correlation between asthma resistance and patients with Pendred Syndrome; the study did not reach statistical significance due to low numbers of participants [70]. In any case, however, none of the Pendred Syndrome patients studied had asthma. It is feasible to assume that specific blockade of pendrin in the respiratory epithelium may open innovative therapeutic avenues in the treatment of asthma and COPD.

In conclusion, it has become evident that pendrin is involved in asthma and COPD. The role of the anion transporter regarding pathogenesis of these diseases is still unclear, thus warranting further, in-depth investigations of pendrin function in the airway epithelium.


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## References


1 Mount DB, Romero MF: The SLC26 gene family of multifunctional anion exchangers. Pflugers Arch 2004;447:710-721.

2 Royaux IE, Suzuki K, Mori A, Katoh R, Everett LA, Kohn LD, Green ED: Pendrin, the protein encoded by the Pendred syndrome gene (PDS), is an apical porter of iodide in the thyroid and is regulated by thyroglobulin in FRTL-5 cells. Endocrinology 2000;141:839-845.

3 Scott DA, Wang R, Kreman TM, Sheffield VC, Karniski LP: The Pendred syndrome gene encodes a chloride-iodide transport protein. Nat Genet 1999;21:440-443.

4 Royaux IE, Wall SM, Karniski LP, Everett LA, Suzuki K, Knepper MA, Green ED: Pendrin, encoded by the Pendred syndrome gene, resides in the apical region of renal intercalated cells and mediates bicarbonate secretion. Proc Natl Acad Sci USA 2001;98:4221-4226.

5 Lacroix L, Mian C, Caillou B, Talbot M, Filetti S, Schlumberger M, Bidart JM: $Na^+/I^-$ symporter and Pendred syndrome gene and protein expressions in human extra-thyroidal tissues. Eur J Endocrinol 2001;144:297-302.

6 Di Valentin E, Crahay C, Garbacki N, Hennuy B, Gueders M, Noel A, Foidart JM, Grooten J, Colige A, Piette J, Cataldo D: New asthma biomarkers: Lessons from murine models of acute and chronic asthma. Am J Physiol Lung Cell Mol Physiol 2009;296:L185-197.

7 Kuperman DA, Lewis CC, Woodruff PG, Rodriguez MW, Yang YH, Dolganov GM, Fahy JV, Erle DJ: Dissecting asthma using focused transgenic modeling and functional genomics. J Allergy Clin Immunol 2005;116:305-311.

8 Nakagami Y, Favoreto S, Jr., Zhen G, Park SW, Nguyenvu LT, Kuperman DA, Dolganov GM, Huang X, Boushey HA, Avila PC, Erle DJ: The epithelial anion transporter pendrin is induced by allergy and rhinovirus infection, regulates airway surface liquid, and increases airway reactivity and inflammation in an asthma model. J Immunol 2008;181:2203-2210.

9 Nakao I, Kanaji S, Ohta S, Matsushita H, Arima K, Yuyama N, Yamaya M, Nakayama K, Kubo H, Watanabe M, Sagara H, Sugiyama K, Tanaka H, Toda S, Hayashi H, Inoue H, Hoshino T, Shiraki A, Inoue M, Suzuki K, Aizawa H, Okinami S, Nagai H, Hasegawa M, Fukuda T, Green ED, Izuhara K: Identification of pendrin as a common mediator for mucus production in bronchial asthma and chronic obstructive pulmonary disease. J Immunol 2008;180:6262-6269.

10 Nofziger C, Vezzoli V, Dossena S, Schonherr T, Studnicka J, Nofziger J, Vanoni S, Stephan S, Silva ME, Meyer G, Paulmichl M: STAT6 links IL-4/IL-13 stimulation with pendrin expression in asthma and chronic obstructive pulmonary disease. Clin Pharmacol Ther 2011;90:399-405.

11 Pedemonte N, Caci E, Sondo E, Caputo A, Rhoden K, Pfeffer U, Di Candia M, Bandettini R, Ravazzolo R, Zegarra-Moran O, Galietta LJ: Thiocyanate transport in resting and IL-4-stimulated human bronchial epithelial cells: Role of pendrin and anion channels. J Immunol 2007;178:5144-5153.

12 Rillema JA, Hill MA: Pendrin transporter carries out iodide uptake into MCF-7 human mammary cancer cells. Exp Biol Med (Maywood) 2003;228:1078-1082.

13 Bidart JM, Lacroix L, Evain-Brion D, Caillou B, Lazar V, Frydman R, Bellet D, Filetti S, Schlumberger M: Expression of $Na^+/I^-$ symporter and Pendred syndrome genes in trophoblast cells. J Clin Endocrinol Metab 2000;85:4367-4372.

14 Suzuki K, Royaux IE, Everett LA, Mori-Aoki A, Suzuki S, Nakamura K, Sakai T, Katoh R, Toda S, Green ED, Kohn LD: Expression of PDS/pds, the Pendred syndrome gene, in endometrium. J Clin Endocrinol Metab 2002;87:938-941.

15 Alesutan I, Pelzl L, C L, Voelkl J, Nofziger C, Dossena S, Paulmichl M, Lang F: Impact of bicarbonate, ammonium chloride, and acetazolamide on hepatic and renal Slc26a4 transcription. Cell Physiol Biochem 2011;28:553-558.

16 Dror AA, Politi Y, Shahin H, Lenz DR, Dossena S, Nofziger C, Fuchs H, Hrabe de Angelis M, Paulmichl M, Weiner S, Avraham KB: Calcium oxalate stone formation in the inner ear as a result of an Slc26a4 mutation. J Biol Chem 2010;285:21724-21735.

17 Everett LA, Belyantseva IA, Noben-Trauth K, Cantos R, Chen A, Thakkar SI, Hoogstraten-Miller SL, Kachar B, Wu DK, Green ED: Targeted disruption of mouse pds provides insight about the inner-ear defects encountered in Pendred syndrome. Hum Mol Genet 2001;10:153-161.

18 Everett LA, Glaser B, Beck JC, Idol JR, Buchs A, Heyman M, Adawi F, Hazani E, Nassir E, Baxevanis AD, Sheffield VC, Green ED: Pendred syndrome is caused by mutations in a putative sulphate transporter gene (PDS). Nat Genet 1997;17:411-422.

19 Morgans ME, Trotter WR: Association of congenital deafness with goitre; the nature of the thyroid defect. Lancet 1958;1:607-609.

20 Izuhara K, Ohta S, Shiraishi H, Suzuki S, Taniguchi K, Toda S, Tanabe T, Yasuo M, Kubo K, Hoshino T, Aizawa H: The mechanism of mucus production in bronchial asthma. Curr Med Chem 2009;16:2867-2875.

21 Lewis CC, Yang JY, Huang X, Banerjee SK, Blackburn MR, Baluk P, McDonald DM, Blackwell TS, Nagabhushanam V, Peters W, Voehringer D, Erle DJ: Disease-specific gene expression profiling in multiple models of lung disease. Am J Respir Crit Care Med 2008;177:376-387.

22 The global burden of disease: 2004 update. Geneva, Switzerland, World Health Organization, 2008.

23 World health statistics 2008. Geneva, Switzerland, WHO Press, 2008.

24 Akinbami LJ, Moorman JE, Liu X: Asthma prevalence, health care use, and mortality: United States, 2005-2009. Natl Health Stat Report 2011:1-14.

25 "The costs of asthma", Asthma and Allergy Foundation 1992 and 1998 Study, 2000.

26 Silva GE, Sherrill DL, Guerra S, Barbee RA: Asthma as a risk factor for COPD in a longitudinal study. Chest 2004;126:59-65.

27 Han MK: Update in chronic obstructive pulmonary disease in 2010. Am J Respir Crit Care Med 2011;183:1311-1315.

28 Holgate ST: Pathophysiology of asthma: What has our current understanding taught us about new therapeutic approaches? J Allergy Clin Immunol 2011;122:495-505.

29 Scanlon PD: The pathogenesis and pathology of COPD: Identifying risk factors and improving morbidity and mortality. Advanced Studies in Medicine 2004;4:S744-749.

30 Chung KF, Adcock IM: Multifaceted mechanisms in COPD: Inflammation, immunity, and tissue repair and destruction. Eur Respir J 2008;31:1334-1356.

31 Turner J, Jones CE: Regulation of mucin expression in respiratory diseases. Biochem Soc Trans 2009;37:877-881.

32 Holgate ST: Pathogenesis of asthma. Clin Exp Allergy 2008;38:872-897.

33 Wills-Karp M, Luyimbazi J, Xu X, Schofield B, Neben TY, Karp CL, Donaldson DD: Interleukin-13: Central mediator of allergic asthma. Science 1998;282:2258-2261.

34 Mullings RE, Wilson SJ, Puddicombe SM, Lordan JL, Bucchieri F, Djukanovic R, Howarth PH, Harper S, Holgate ST, Davies DE: Signal transducer and activator of transcription 6 (STAT-6) expression and function in asthmatic bronchial epithelium. J Allergy Clin Immunol 2001;108:832-838.

35 Lee YC, Lee KH, Lee HB, Rhee YK: Serum levels of interleukins (IL)-4, IL-5, IL-13, and interferon-gamma in acute asthma. J Asthma 2001;38:665-671.

36 Matsumoto K, Taki F, Miura M, Matsuzaki M, Takagi K: Serum levels of soluble IL-2R, IL-4, and soluble Fc epsilon RII in adult bronchial asthma. Chest 1994;105:681-686.

37 ten Hacken NH, Oosterhoff Y, Kauffman HF, Guevarra L, Satoh T, Tollerud DJ, Postma DS: Elevated serum interferon-gamma in atopic asthma correlates with increased airways responsiveness and circadian peak expiratory flow variation. Eur Respir J 1998;11:312-316.

38 Joseph J, Benedict S, Al-sowaidi S, Joseph M, Zoubeidi T: Serum interleukin-13 levels are elevated in mild and moderate persistent asthma. The Internet Journal of Asthma, Allergy and Immunology 2005;4

39 Ohshima Y, Katamura K, Miura M, Mikawa H, Mayumi M: Serum levels of interleukin 4 and soluble CD23 in children with allergic disorders. Eur J Pediatr 1995;154:723-728.

40 Zheng KC, Nong DX, Morioka T, Todoriki H, Ariizumi M: Elevated interleukin-4 and interleukin-6 in rats sensitized with toluene diisocyanate. Ind Health 2001;39:334-339.

41 Zund G, Madara JL, Dzus AL, Awtrey CS, Colgan SP: Interleukin-4 and interleukin-13 differentially regulate epithelial chloride secretion. J Biol Chem 1996;271:7460-7464.

42 Danahay H, Atherton H, Jones G, Bridges RJ, Poll CT: Interleukin-13 induces a hypersecretory ion transport phenotype in human bronchial epithelial cells. Am J Physiol Lung Cell Mol Physiol 2002;282:L226-236.

43 Galietta LJ, Pagesy P, Folli C, Caci E, Romio L, Costes B, Nicolis E, Cabrini G, Goossens M, Ravazzolo R, Zegarra-Moran O: IL-4 is a potent modulator of ion transport in the human bronchial epithelium *in vitro*. J Immunol 2002;168:839-845.

44 Woodruff PG, Boushey HA, Dolganov GM, Barker CS, Yang YH, Donnelly S, Ellwanger A, Sidhu SS, Dao-Pick TP, Pantoja C, Erle DJ, Yamamoto KR, Fahy JV: Genome-wide profiling identifies epithelial cell genes associated with asthma and with treatment response to corticosteroids. Proc Natl Acad Sci USA 2007;104:15858-15863.

45 Zhou Y, Dong Q, Louahed J, Dragwa C, Savio D, Huang M, Weiss C, Tomer Y, McLane MP, Nicolaides NC, Levitt RC: Characterization of a calcium-activated chloride channel as a shared target of Th2 cytokine pathways and its potential involvement in asthma. Am J Respir Cell Mol Biol 2001;25:486-491.

46 Merves M, Krane CM, Dou H, Greinwald JH, Menon AG, Choo D: Expression of aquaporin 1 and 5 in the developing mouse inner ear and audiovestibular assessment of an AQP5 null mutant. J Assoc Res Otolaryngol 2003;4:264-275.

47 Wang K, Feng YL, Wen FQ, Chen XR, Ou XM, Xu D, Yang J, Deng ZP: Decreased expression of human aquaporin-5 correlated with mucus overproduction in airways of chronic obstructive pulmonary disease. Acta Pharmacol Sin 2007;28:1166-1174.

48 Shen Y, Wang Y, Chen Z, Wang D, Wang X, Jin M, Bai C: Role of aquaporin 5 in antigen-induced airway inflammation and mucous hyperproduction in mice. J Cell Mol Med 2011;15:1355-1363.

49 Garnett JP, Hickman E, Burrows R, Hegyi P, Tiszlavicz L, Cuthbert AW, Fong P, Gray MA: Novel role for pendrin in orchestrating bicarbonate secretion in CFTR-expressing airway serous cells. J Biol Chem 2011; in press.

50 Schindler U, Wu P, Rothe M, Brasseur M, McKnight SL: Components of a Stat recognition code: Evidence for two layers of molecular selectivity. Immunity 1995;2:689-697.

51 Lappalainen U, Whitsett JA, Wert SE, Tichelaar JW, Bry K: Interleukin-1beta causes pulmonary inflammation, emphysema, and airway remodeling in the adult murine lung. Am J Respir Cell Mol Biol 2005;32:311-318.

52 Harper RW, Xu C, Eiserich JP, Chen Y, Kao CY, Thai P, Setiadi H, Wu R: Differential regulation of dual NADPH oxidases/peroxidases, duox1 and duox2, by Th1 and Th2 cytokines in respiratory tract epithelium. FEBS Lett 2005;579:4911-4917.

53 Rada B, Lekstrom K, Damian S, Dupuy C, Leto TL: The pseudomonas toxin pyocyanin inhibits the dual oxidase-based antimicrobial system as it imposes oxidative stress on airway epithelial cells. J Immunol 2008;181:4883-4893.

54 Mullane K: Asthma translational medicine: Report card. Biochem Pharmacol 2011;82:567-585.

55 Barnes PJ: New therapies for asthma: Is there any progress? Trends Pharmacol Sci 2010;31:335-343.

56 Wenzel S, Wilbraham D, Fuller R, Getz EB, Longphre M: Effect of an interleukin-4 variant on late phase asthmatic response to allergen challenge in asthmatic patients: Results of two phase 2a studies. Lancet 2007;370:1422-1431.

57 McCusker CT, Wang Y, Shan J, Kinyanjui MW, Villeneuve A, Michael H, Fixman ED: Inhibition of experimental allergic airways disease by local application of a cell-penetrating dominant-negative STAT-6 peptide. J Immunol 2007;179:2556-2564.

58 Kinyanjui MW, Fixman ED: Cell-penetrating peptides and proteins: New inhibitors of allergic airways disease. Can J Physiol Pharmacol 2008;86:1-7.

59 Healey GD, Zinnen S, Lockridge JA, Richards I, Evans N, Walker W: Identification of small interfering RNA targeting signal transducer and activator of transcription 6: Characterisation and selection of candidates for pre-clinical development. J RNAi Gene Silencing 2010;6:401-410.

60 Chiba Y, Todoroki M, Nishida Y, Tanabe M, Misawa M: A novel STAT6 inhibitor AS1517499 ameliorates antigen-induced bronchial hypercontractility in mice. Am J Respir Cell Mol Biol 2009;41:516-524.
61 Holmes AM, Solari R, Holgate ST: Animal models of asthma: Value, limitations and opportunities for alternative approaches. Drug Discov Today 2011;16:659-670.
62 Canning BJ: Modeling asthma and COPD in animals: A pointless exercise? Curr Opin Pharmacol 2003;3:244-250.
63 Corren J, Lemanske RF, Hanania NA, Korenblat PE, Parsey MV, Arron JR, Harris JM, Scheerens H, Wu LC, Su Z, Mosesova S, Eisner MD, Bohen SP, Matthews JG: Lebrikizumab treatment in adults with asthma. N Engl J Med 2011;365:1088-1098.
64 Bai TR, Knight DA: Structural changes in the airways in asthma: Observations and consequences. Clinical Science 2005;108:463-477.
65 Baraldo S, Turato G, Bazzan E, Ballarin A, Damin M, Balestro E, Oliani KL, Calabrese F, Maestrelli P, Snijders D, Barbato A, Saetta M: Non-eosinophilic asthma in children: Relation with airway remodeling. Eur Respir J 2011;38:575-583.
66 Barbato A, Turato G, Baraldo S, Bazzan E, Calabrese F, Panizzolo C, Zanin ME, Zuin R, Maestrelli P, Fabbri LM, Saetta M: Epithelial damage and angiogenesis in the airways of children with asthma. Am J Respir Crit Care Med 2006;174:975-981.
67 Holgate ST: The sentinel role of the airway epithelium in asthma pathogenesis. Immunol Rev 2011;242:205-219.
68 Dossena S, Vezzoli V, Cerutti N, Bazzini C, Tosco M, Sironi C, Rodighiero S, Meyer G, Fascio U, J FUR, Ritter M, Fugazzola L, Persani L, Zorowka P, Storelli C, Peccoz PB, Botta G, Paulmichl M: Functional characterization of wild-type and a mutated form of SLC26A4 identified in a patient with Pendred syndrome. Cell Physiol Biochem 2006;17:245-256.
69 Nakano T, Inoue H, Fukuyama S, Matsumoto K, Matsumura M, Tsuda M, Matsumoto T, Aizawa H, Nakanishi Y: Niflumic acid suppresses interleukin-13-induced asthma phenotypes. Am J Respir Crit Care Med 2006;173:1216-1221.
70 Madeo AC, Manichaikul A, Pryor SP, Griffith AJ: Do mutations of the Pendred syndrome gene, SLC26A4, confer resistance to asthma and hypertension? J Med Genet 2009;46:405-406.