Review Article

Epithelial Sodium and Chloride Channels and Asthma

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Abstract

Objective: To focus on the asthmatic pathogenesis and clinical manifestations related to epithelial sodium channel (ENaC)/chlorine ion channel.

Data Sources: The data analyzed in this review were the English articles from 1980 to 2015 from journal databases, primarily PubMed and Google Scholar. The terms used in the literature search were: (1) ENaCs; cystic fibrosis (CF) transmembrane conductance regulator (CFTR); asthma/asthmatic, (2) ENaC/sodium salt; CF; asthma/asthmatic, (3) CFTR/chlorine ion channels; asthma/asthmatic, (4) ENaC/sodium channel/scnn1a/scnn1b/scnn1g/scnn1d/amiloride-sensitive/amiloride-inhibtable sodium channels/sodium salt; asthma/asthmatic, lung/pulmonary/respiratory/tracheal/alveolar, and (5) CFTR; CF; asthma/asthmatic (ti).

Study Selection: These studies included randomized controlled trials or studies covering asthma pathogenesis and clinical manifestations related to ENaC/chlorine ion channels within the last 25 years (from 1990 to 2015). The data involving chronic obstructive pulmonary disease and CF obtained from individual studies were also reviewed by the authors.

Results: Airway surface liquid dehydration can cause airway inflammation and obstruction. ENaC and CFTR are closely related to the airway mucociliary clearance. Ion transporters may play a critical role in pathogenesis of asthmatic exacerbations.

Conclusions: Ion channels have been the center of many studies aiming to understand asthmatic pathophysiological mechanisms or to identify therapeutic targets for better control of the disease.

Key words: Airway Surface Liquid; Asthma; Cystic Fibrosis Transmembrane Conductance Regulator; Epithelial Sodium Channel; Mucociliary Clearance

Introduction

Asthma is a common chronic disease of children and adults which is characterized by airway inflammation, hyperreactivity, mucus overproduction and airway obstruction.[1,2] The airway epithelial cell is a prominent contributor to asthmatic exacerbations. Epithelial cell mucus production is increased in asthma,[3] and plugging of the airways with mucus is prominent and sometimes fatal for severe asthma exacerbations.[4] Airway epithelial cells also play central roles in the response to allergens. In this setting, T-helper 2 (Th_2) cells and other cells produce interleukin-13 (IL-13) and IL-4, cytokines those act directly on airway epithelial cells to induce mucus production and airway hyperreactivity.[5-7]

Changes in the airway surface liquid (ASL) that covers the epithelium can cause airway disease. ASL is comprised of a mucus layer and a periciliary layer.[8] Ciliary beating and coughing propel ASL toward the upper airways thereby removing mucus and inhaled pathogens and particles.[9] ASL thickness is regulated by active ion transport across epithelial cells.[10] In cystic fibrosis (CF), mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene result in decreased chloride secretion, which leads to ASL dehydration, impaired mucus clearance, and airway inflammation and obstruction.[11] Similar pathology was seen with ASL dehydration in mice with transgenic overexpression of the epithelial sodium channel (ENaC).[12] Changes in ion transport have also been implicated in asthma pathogenesis. IL-13 or IL-4 stimulation alters chloride conductance and converts human bronchial epithelial cells from an absorptive to a secretory phenotype, which may help to "flush" particulates and mucus from the airway lumen.[13]

Both airway hyperreactivity and inflammation have been shown to be influenced by ASL hydration in various models.[12,14] Mechanistic relationships among ASL hydration, airway inflammation, and airway obstruction and hyperreactivity are complex and incompletely understood

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despite extensive analysis of various asthma and CF models. It is clear that airway epithelial cells can affect inflammation by producing cytokines that affect maturation and recruitment of eosinophils and other leukocytes.[15] Ion channel regulator could be an effective strategy for treatment of asthma exacerbations.[16,17] The results reported provide a basis for future studies aimed at developing and testing pendrin inhibitors for use in asthma exacerbations. Therefore, extensive researches on the channel that contributed to the genesis or therapy of the disease have been carried out over the last 30 years. The review focus on ENaC/chlorine ion channel associated with asthma pathogenesis and clinical manifestations has been evaluated in molecular, genetic, animal model or human studies.

The Characteristics of Sodium/Chloride Channel Proteins of Respiratory Epithelial Cells

The conducting airways are the primary interface between the extracellular environment and the lung, which play a major role in host defense.[18-20] Mucus clearance is a central component of the innate defense system of the lung.[21-23] During normal mucus clearance, inhaled pathogens and particles become trapped in the mucus layer and are then expelled before they can colonize in the airways.[24] The rate of mucociliary clearance (MCC) is strongly influenced by the hydration state of the ASL and mucus layers.[25] Mucus hydration is set by the volume of liquid present on the airway surfaces, which may be modified by active ion transport processes in both the superficial epithelium and glands.[26-29] Secretion is mediated by the apical membrane Cl^- channels (CFTR)[30,31] while absorption requires ENaC.[32] Ion channels, including CFTR and ENaC, play a significant role in the maintenance of ASL.[33,34]

Molecular cloning has confirmed that the sodium channel (ENaC) has α, β, γ and δ subunits in mammalian respiratory epithelial. ENaC belongs to the voltage independent ion channels. Nevertheless, channels are highly selective for Na^+ over K^+ ions. The selection makes Na^+ by adapting transmembrane ion concentration.[35]

Epithelial sodium channel participates in maintaining appropriate salt and water balance by reabsorbing Na^+ at the apical membrane, thereby creating an osmotic gradient that facilitates the reabsorption of fluid[36] [Figure 1]. In the lung, ENaC activity plays an important role in maintaining ASL volume within normal limits.

The CFTR is a kind of Cl^- channel in epithelial membrane regulated by phosphorylation, which is located primarily in the airway epithelial cells of apical membrane [Figure 1]. Due to its help of the Cl^- and HCO_3^- travel across the plasma membrane and epithelial salt transport, it plays an important role in regulating water flow and ion concentration, and adjusting the pH value of mucus. Patients with CFTR functional defects have low efficiency in mucus secretion, mucus clearance, and mucus transport, which may easy to induce airway inflammation and airway mucus plugs.[37,38]

Cystic fibrosis transmembrane conductance regulator as cAMP dependent Cl^- channel, also controls the other type of ion channels, including epithelial Cl^- and Na^+ channels, and ATP transporter. Studies have reported oxidant stress affect the secretion of Cl^- and the function of CFTR. In addition, CFTR regulates the activity of ENaC. ENaC interact with CFTR, CFTR could down-regulate ENaC in physiological conditions and compromise the function of ENaC. Nevertheless, it could mutate in pathological condition, which enhances ENaC's function, raises the expression of CFTR.[39-41]

The Epithelial Sodium/Chloride Channel and Bronchial Asthma

Asthma is associated with airway hyperresponsiveness (AHR), which leads to recurrent episodes of shortness of breath, coughing, and wheezing. At the pathophysiological level, asthma results from complex biological interactions between different cell types, both resident (i.e., epithelial and smooth muscle cells) and circulating (mainly immune cells), and environmental factors such as allergens, infections, and tobacco smoke.[42] A key element in this pathophysiological process is the TH_2 cell, which orchestrates chronic inflammation, smooth muscle contraction, and airway remodeling.[43] Another key feature is a defective airway epithelium, facilitating allergen contact with mucosal antigen-presenting dendritic cells, which in turns will promote a TH_2 cell phenotype.[44-46]

Airway epithelial transports water and salt as conduction. The channel response of osmotic pressure and mucus cilia clearance is associated with the activity of ion channels. CFTR and ENaC, as an important channel for epithelial fluid and electrolyte transport, play a key role in the AHR diseases. Ion channels also play a key role in the process of the asthmatic attacking. It is closely related to the repair process and airway remodeling after epithelial inflammatory damage. In the pathophysiological process of asthma, ion channel regulates many key functions. Early studies of asthma mainly concentrated in the role of the contraction of airway smooth muscle (ASM). Recent research has focused on epithelial electrolyte disorder. ENaC and CFTR participate in airway epithelial permeation, repair and barrier function in the airway. CFTR dysfunction caused by the change of the Cl^- and Na^+ channel activity lead to airway mucus obstruction, infection and inflammation. Abnormal epithelial mucus secretion increases in asthma, at the same time epithelial injury induces AHR, aggravate airway remodeling.[47-49]

Cl^- is one of the most abundant anions, chloride ion channel is distributed in cell membranes and organelles membrane as a transmembrane protein. It is generally a multiple transmembrane structure composed of several domains. In addition to the CFTR, Cl^- channel-gating depends on many factors, including transmembrane voltage, cell swelling, cross-linking with signal molecules, cell phosphorylation residue or ATP combination and hydrolysis caused by

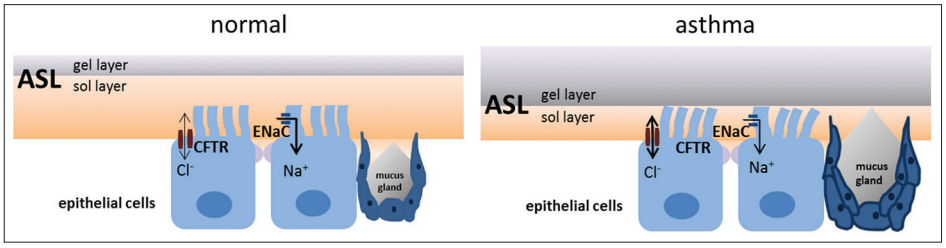

Figure 1: The airway epithelium shows ENaC/CFTR associated with asthma pathophysiology.

various ions and protein kinase. On the one hand, it is associated with the electric charge transport, such as current flows in the channel. It is also associated with the transport of material.[50-52] For example, Cl^- current in cytoplasmic membrane is very important for adjusting the excitability of nerve and muscle, in addition, in the acute attack of asthma. One mechanism of atomization inhalation drug therapy is increasing the expression of ENaC. The current flow in intracellular Cl^- channel not only guarantees H^+-ATPase electrically neutral transport in the lacuna of some cell but also is very important for regulating cell capacity. At the same time, blood pH value increases, serum lactic acid levels decrease, which are beneficial for the body recover.[53]

In the airways, ion channels have been linked to tight junction formation, epithelial permeability, or repair, considering that these ion channel-dependent cell processes are common denominators in asthma pathophysiology, their study (either measuring function or expression levels) in asthmatic airways or in animal models may provide novel insights into the pathogenesis of the disorder.[54,55]

The airway epithelium shows ENaC/CFTR associated with asthma pathophysiology [Figure 1].

Epithelial Cells Sodium/Chloride Channel and High Airway Mucus Secretion (Airway Surface Liquid)

An important feature of asthma is excessive hyperplasia of goblet cells and mucus secretion that are key features contributing to airflow obstruction in the clinical syndrome of asthma. Mucus causes small airway obstruction and airway hyperresponsive which is difficult to remove. Previous *in vitro* studies demonstrated that Th_2 cytokines act as potent modulators of epithelial ion transport and fluid secretion.[56,57] Autopsy showed that the airway in patients with acute asthma deaths has excessive hyperplasia of goblet cells and secretion of mucus. The excessive airway mucus secretion is one of the leading causes of death in severe asthma. Studies have also confirmed that the excessive mucus secretion is an independent risk factor for the decline of forced expiratory volume in 1 s in asthmatic patients.[58]

Respiratory epithelial sodium channels with high airway mucus secretion

Na^+ and Cl^- channel in respiratory epithelium control water and salt transport across the membrane to adjust the ASL composition, thickness, and mucus-cilium swings. ENaC is distributed in cavity roof membrane in epithelial cells in all levels of the respiratory tract (from the nasopharynx to bronchioles). It has tissue specificity in respiratory ENaC and is regulated with local, systemic and genetic factors, and it is mainly responsible for maintaining the volume of ASL (thickness). The active transport of Na^+ is divided into two stages; first of all, Na^+ on the cell basal surface has been actively transported from cytoplasm to the stroma, resulting in electrochemical gradient which prompted Na^+ from lumen on the top surface transferred to the cytoplasm by ENaC. The osmotic pressure of Na^+ transport drives the water molecules across the membrane as passive transport[59,60] [Figure 1]. Pseudo-hypoaldosteronism patients have decreased sodium reabsorption function and increased watery secretion, 99m-Tc scanning suggests mucosa of the abnormal-lung cilia showed greater clearance rate.[61] In addition to the disorder of secretion in Cl^-, patients with lung CF have enhanced reabsorption function of ENaC which easily lead to bacterial engraftment and infection.

Blocking ENaC may reduce airway water reabsorption, and increase mucus moist. As amiloride, an ion channel regulator by inhibition of sodium reabsorption of epithelial cells and the secretion of chloride ion, can maintain hydration of epithelial cells on the surface, promote the role of mucous blanket mobile.[62]

Cl^- channel of respiratory epithelial cells and airway surface liquid high secretion

Epithelial Cl^- channel is distributed in airway epithelial cells and the top of the cavity of submucosal cell, including cAMP-activated Cl^- channels and Ca^{2+} activated Cl^- channels. The former is also called CFTR, which could reduce the secretion of Cl^- when mutations happened, leading to secondary water reduction within cavity passage, increased proportion of water and salt in mucin, and sticky mucus. The latter is called calcium-activated chloride channel (CaCC) channel, the channel has a very close relationship with asthma goblet cell hyperplasia, excessive airway mucus secretion, mucin gene expression and high reactivity in the airway. A number of studies have shown that blocking CaCC gene can reduce the expression of mucin gene and the mucus secretion.[63]

Adjust sodium/chloride channel expression for the treatment of asthma in clinical practice

Epithelial sodium channel in airway epithelia is mainly

regulated by glucocorticoids (GCs). Its expression is linked to changes in inflammation rather than changes in blood pressure/volume.[64,65] ENaC can also be controlled by intracellular factors including pH, lipids, and protein kinase A (PKA),[66-68] which may affect the number of ENaCs inserted into the plasma membrane as well as affect gating.[69] GC can influence the expression of ENaC. It can be combined with specific GC receptor (GR) in the cell, which makes the GR complex dissociate, then GR is transferred to the nucleus to combine with GRBS (GC response element) of the DNA. It regulates the expression of ENaC at the level of transcription, translation after transcription and protein. The main physiological channels for activating ion channels are increased receptor-mediated cAMP and secondary activation of PKA. In the acute asthma attacking, the mechanism of systemic or local GC is to increase the intracellular cAMP, phosphorylate cell, to enhance ENaC expression and to increase its function.[70,71]

Sodium-water transport with ENaC is a process of energy consumption, in case of lack of oxygen, it can increase the intracellular reactive oxygen content, the shortage of the energy will bring down the role of ENaC. Ulinastatin can be used to reverse the inhibition of ENaC-αmRNA and protein expression due to the lack of oxygen, and has some relevance with the concentration. In these drugs those regulate the function of ENaC, β agonists can make the ENaC gene expression increased, promote the protein phosphorylation, and inhibit the degradation of ENaC.[72] It has been reported the specific chloride channel inhibitors not only inhibit the IL-13 induction of goblet cell hyperplasia, but also suppress the AHR and the infiltration of eosinophilic.[73]

Anagnostopoulou *et al*.[74] demonstrate that allergic inflammation enhanced basal Cl^- secretion in both airway regions and inhibited ENaC-mediated Na^+ absorption and increased Ca^{2+}-dependent Cl^- secretion in bronchi. Allergen-induced alterations in bronchial ion transport were associated with reduced transcript ENaC levels. Studies demonstrate that Th_2-dependent airway inflammation produced a pro-secretory ion transport phenotype *in vivo*. These results suggest that Th_2-mediated fluid secretion may improve airway surface hydration and clearance of mucus that is hypersecreted in allergic airway diseases such as asthma. These results indicate that the coordinate increase in fluid and mucin secretion in Th_2-driven airway inflammation may provide a protective mechanism to promote mucus clearance and prevent airway mucus plugging in the presence of mucus overproduction in allergic airway disease. It suggests that dysregulation of this epithelial response may provide a clue to severe airway mucus plugging in fatal asthma.[74] Taken together, these studies suggested that selected Th_2 cytokines may be involved in the regulation of ASL volume to improve mucus hydration and promote MCC in allergic airway disease.

Respiratory epithelial cells and refractory asthma

Epithelial cell injury is the typical characteristics in asthma airway with chronic inflammation. Airway remodeling is the important pathogenesis of refractory asthma. The information exchange between airway epithelial cells and immune inflammatory cells may play an important role in the local mucosal regulation of the immune system. The remodeling of epithelial cells during the repair process after injury could cause a new signal transduction pathway, shielding the body's normal T-cell immune tolerance mechanism-induced by the allergens thus promote the development of the local mucosal immune inflammation. The change of highly active genes within the network and its environment may induce it to form new genes in epithelia cells and new molecular link between airway mucosal immunity and inflammation which may be important for the development of refractory asthma. Researches have shown the relation between epithelial cells and smooth muscle cells, it may involve with ion channel transport, which still needs further research.

The Relationship Among Dietary Salt Intake, Sodium of Blood and Urine, Epithelial Sodium Channel/Cystic Fibrosis Transmembrane Conductance Regulator and Asthma

Studies have shown that dietary salt intake, sodium of blood and urine affect ENaC expression, is intimately related to the onset of hypertension, likewise, it has relation with the asthma attack and its phenotypic.

Dietary salt intake, blood urine sodium and airway hyperresponsiveness and allergy

The data from studies examining airway function in the context of asthma and dietary salt intake demonstrate a weak association between salt intake and increased airway reactivity and are controversial. Epidemiological studies have reported increase in asthma mortality rate is associated with high salt intake. In addition, the use of histamine excitation for measuring shows that airway reactivity is related to the rise in 24 h urine sodium secretion.[75] Britton *et al*.[76] and Devereux *et al*.'s[77] studies were not observed the correlation between 24 h urine sodium secretion and airway reactivity.

Furthermore, extensive studies of the plasma of individuals with allergic asthma and/or allergic rhinitis revealed the existence of a hematogenous factor that leads to the accumulation of Na^+ within platelets, reduces the absorption of the cation, as well as the Na^+/K^+ pump common activity. Serum from allergic individuals could inhabit their absorption of cation in anallergic individuals. Interestingly, there has good correlation between plasma suppression level and the degree of observed airway reactivity.[78]

The researchers also found that allergic is associated with the change of intracellular Na^+ homeostasis. Tribe *et al*.[78] reported that levels of Na^+ influx into isolated peripheral blood mononuclear cells (PBMCs) were associated with the levels of airway responsiveness. These data were confirmed by two more recent studies that reported an association between Na^+/K^+ pump inhibition and resulting intracellular

Na^+ accumulation and increased severity of airway dysfunction. It is apparent that allergy is associated with elevated serum levels of an endogenous inhibitor of the Na^+/K^+ pump, which can lead to an accumulation of intracellular Na^+ associated with atopy. Thus, it may contribute to airway dysfunction by elevating cytosolic levels of Na^+, thereby promoting Ca^{2+} influx via reverse-mode Na^+/Ca^{2+} activity and increasing tone. In addition, contraction of ASM, the association also has limitations, this phenomenon does not seem to be limited to airway dysfunction associated with atopy. The exact nature of the hematogenous factor associated with inhibition of the Na^+/K^+ pump in allergy has yet to be completely elucidated. Some have suggested that lysophosphatidylcholine (LPC) may be a likely candidate. High-serum LPC levels have been associated with increased asthma severity and increased accumulation of Na^+ in PBMCs and leukocytes.

Dietary Na^+ and inflammation in exercise-induced airway hyperresponsiveness

During ventilation, inhaled air is conditioned (i.e., warmed and humidified) by contact with the inner epithelial layer and its associated mucous coating. When the intensity of ventilation increases, as during exercise, the conditioning capacity of the airways is taxed, resulting in a reduced capacity to humidify inhaled air and an increase in mucosal osmolarity (i.e., mucous dehydration). The net result of airway dehydration is the activation of resident airway inflammatory cells (e.g., mast cells) and increasing the release of inflammatory mediators (e.g., histamine, leukotrienes, and prostaglandins) that trigger contraction of the ASM.

Although the role of dietary sodium in the modulation of asthma, its associated AHR is unclear. Recent evidence suggests that dietary sodium can potentiate exercise-induced bronchoconstriction (EIB). Gotshall *et al*.[79] reported that low-salt diets improved and high-salt diets worsened postexercise pulmonary function in individuals with diagnosed EIB (or exercise-induced asthma) as measured by spirometry. Mickleborough and Fogarty[75] reported that high-salt diets decreased arterial blood oxygen saturation during intense exercise (i.e., 90% of predicted maximum heart rate in individuals with EIB). In a well-designed follow-up study (double-blinded placebo-controlled trial), it was revealed that a low-salt diet attenuates some of the inflammation associated with EIB (e.g., attenuation of increases in sputum levels of eosinophil cation protein, IL-1, and IL-8 but not cysteinyl leukotrienes C_4-E_4, leukotriene B_4, or prostaglandin D_2-methoxime).

Taken together, it appears that increases in dietary salt may worsen the inflammatory status in the airways of individuals with EIB, leading to the release of mediators that trigger contraction of the ASM, thus resulting in airway dysfunction. This may act in concert with changes in mucous osmolarity that decrease the ability of the airways to condition inhaled air. So far, the mechanism by which sodium is increasing inflammation is unknown. Both atopy and high-salt diets are associated with altered cellular Na^+ homeostasis that appears to result from an inhibition of the Na^+/K^+ pump.[80-82] Dietary sodium alters airway function by elevating systemic levels of endogenous ouabain that in turn inhibit the Na^+/K^+ pump. The resulting accumulation of Na^+ within ASM cells triggers membrane depolarization and Ca^{2+} influx via the reverse-mode of the Na^+/Ca^{2+}. Future population studies must consider the possibility that the level of airway dysfunction observed in response to salt loading may vary considerably, just as is observed in salt-sensitive hypertension. In addition, to elucidate the mechanism of this effect, investigations will need to pay more attention to salt sensitive airway obstruction in the future.

Association of Cystic Fibrosis Transmembrane Conductance Regulator Gene with Asthma

Cystic fibrosis transmembrane conductance regulator gene mutation with asthma

The most common diseases associated with CFTR are asthma. The CFTR gene mutations and the Cl^- channel function disorder have been confirmed that affect the phenotype of asthma directly or indirectly, but the results are different for different people.

Dahl *et al*.[83] found a significant association between asthma and ΔF508 heterozygosity and concluded that ΔF508 heterozygosity is over-represented among asthmatics. In the same year, Lowenfels *et al*.[84] conducted a multinational analysis in 1113 obligate CFTR gene mutation heterozygotes and 688 controls and found that prevalence of asthma in CF heterozygotes was 9.6% that was similar with that reported by Dahl *et al*.[83] A Greek population study result also shows the involvement of CFTR gene in asthma.[85] Ngiam *et al*.[86] revealed the potential relationship between CFTR gene mutation in Asian patients (Singaporean Chinese) with severe asthma. Significantly higher frequency of CFTR mutations among patients with unaffected controls suggests that these mutations may increase the risk for disease. However, the studies in Barcelona found no obvious correlation between both.[87]

In the Norwegian Environment and Childhood Asthma study, no significant association was found in asthma, reduced lung function, bronchial hyperresponsiveness or FeNO levels and CF heterozygosity or the modulating polymorphism. This conclusion is consistent with the Greek population. In a case–control study conducted in Korea, no significant differences were found in genotype and allele frequencies of the 9 polymorphisms observed between the nonasthma and asthma groups.[88,89]

Several studies done in context with asthma and CFTR gene mutation, have found increased IgE level and positive skin prick test among asthma patients. But these findings do not suggest the association of CFTR gene mutations with atopic asthma as most of the studies observed. It is still needed large sample and detailed phenotypic study in order to clear CFTR role in asthma incidence.

Pathophysiology of asthma in relation with cystic fibrosis transmembrane conductance regulator

Cystic fibrosis transmembrane conductance regulator dysfunction alters physiological functions of both surface and submucosal gland of epithelium, which leads to salt and water imbalance across airway epithelium, depleted surface liquid layer, and impaired MCC. Impaired MCC, together with CFTR-related changes in the airway surface microenvironment, leads to a progressive cycle of infection, inflammation, and declining lung function.[90,91] Lung disease results from clogging of the airways, mucus build-up, decreased MCC and inflammation. Inflammation and infection will cause injury and structural changes to the lungs.[92,93] ASL depletion is believed to cause ciliary collapse and loss of MCC. Poor MCC with excessive mucus production causes obstructive lung disease such as asthma and chronic bacterial infections leading to respiratory failure that is major cause of mortality.

In fact, due to missing or low diagnosis level, CF is considered a rare disease in China, but with the progress of diagnosis technology, there has been increased evidence that the CF exists in China. But we have not conducted CFTR gene mutations and asthma studies yet. In future, we need to pay more attention in the field.

Conclusions

Multiple pathogenic factors such as inflammation, allergy, cytokines, and environment, lead to mucosal ENaC/CFTR abnormalities. Therefore, dysfunction in ion channels changes ASL and the amount of mucus in airway epithelium. CFTR/ENaC channels participate in fluid secretion and reabsorption, and could play a role in pathogenesis of asthma exacerbations. Ion channels have been the center of many studies aiming to understand asthma pathophysiological mechanisms or to identify therapeutic targets for better control of the disease.

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