Review article

Ion channels in obstructive pulmonary disease and their impact on therapy

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Abstract:

Chronic Obstructive Pulmonary Disease (COPD) refers to the progressive lung disorder associated with airway obstruction with mucus overproduction that makes it difficult to breathe. Recent studies have revealed that dysregulation of ion channels plays a prime role in the pathogenesis of COPD. Patients with COPD exhibit reduced Cl- secretion and increased Na+ reabsorption due to perturbed CFTR and ENaC activity leading to viscous mucous secretionassociated with reduced mucociliaryclearance and infection from chronic pathogens that promotes progressive airway inflammation leading to worsening of COPD. The therapeutic strategies aiming at restoring these ion-channel activities by channel modulator(s) would represent an attractive alternative strategy to treat COPD patients. In this present review, we have compared the roles of the key ion-channels as CFTR and ENaC in normal and COPD subjects with special emphasis on alternative calcium activated chloride channel activity in airway epithelia. We have also discussed the regulation of the airway lining fluid and the intact mucociliary clearance system by the function of these important ion channels with special reference towards the better understanding in the pathophysiology of COPD.

Key word : Cystic Fibrosis, COPD, CFTR, CaCC, ENaC

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Abbreviations:

ASL- Airway surface liquid

CaCC- Calcium-activated chloride channel

CF - Cystic Fibrosis

COPD- Chronic obstructive pulmonary disease

CFTR- Cystic fibrosis transmembrane conductance regulator

CS- Cigarettesmoke

EGFR- Epidermal growth factor receptor

ENaC- Epithelial sodium channels

ERK- Extracellular-signal-regulated kinases

PCL- PericiliaryLiquid

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INTRODUCTION:

The two most common respiratory diseases which are estimated to be the third leading cause of death include asthma and chronic obstructive pulmonary disease (COPD). India contributes a significant and growing percentage of chronic respiratory diseases which is estimated to be amongst the highest in the world. COPD generally involves inflammation, mucus production, dysregulation of ion and water transport across the respiratory epithelium, lung parenchymal destruction;all been involved to together to contribute to the airway obstruction. Smoking is by far recognized the main etiological factor for COPD and is believed to account for approximately 90% of the cases. The burden of COPD on the healthcare system is enormous and is estimated to affect over 300 million people worldwide. The estimated economic cost of COPD is also very high. Despite all these facts, the pharmacotherapy available to COPD is mainly symptomatic and cannot really make much change in the natural history of the disease.

In COPD, airway obstruction may be due to i) obstruction inside the airway lumen ii) obstruction from narrowing of the airway because of airway wall thickening (remodelling),and iii) narrowing of the airways from destruction of lung parenchyma that confers radial traction to keep the airway open.Obstruction inside the airway lumen may be a result of occlusion by excessive secretion as occurs in chronic bronchitis phenotype of COPD. Somewhat like asthma, in chronic bronchitis the conducting airways are inflamed chronically by an irritant and swell with heavy mucus secretion. In the respiratory tract, goblet cells secrete mucus onto the epithelial surfaces of the airway to keep the surfaces lubricated that helps prevent diseases by trapping potential invaders. Mucus is a mixture of predominantly water and glycoproteins called mucins. The composition, water content and volume of mucus are controlled by the secretion and absorption of ions (mainly Cl- and Na+) and water across the respiratory epithelium. In normal airways, an appropriate balance of these two ions is maintained by a balance between Na+ absorption and Cl- secretion. The Na+ absorption is mediated by the ENaC (epithelial sodium channel) and Cl- secretion is regulated by the CFTR (cystic fibrosis transmembrane conductance regulator) along with alternative calcium activated chloride channel (CaCC). These ion channels acts synchronously to determine the volume of fluid on airway surfaces. This transport balance regulates the height of the periciliary liquid (PCL) in which cilia beats to permit effective mucus clearance. This process is essential for a healthy lung and is part of the innate immune system. However, defective secretion of Cl- and absorption of Na+ may lead to reduce PCL depth, impede ciliary movement and mucus clearance, and promote airway inflammation and mucus cell hyperplasia. All these pathophysiological changes are characteristically found in COPD. In this short article, we have outlined the role of key ion-channels in the regulation of an intact mucociliary clearance and airway lining fluid and their impact on COPD therapy.

Tran epithelial ion-transport and mucus secretion in respiratory epithelia:

Airways are lined with an epithelium all over except for the very terminal part. The epithelia consist mainly of ciliated cells, clara cells, undifferentiated basal cells, and goblet cells. These cells are expressed in different proportions in different parts of the airway epithelia, and their local distribution varies as shown in figure 1. The frequency of ciliated cells increase progressively towards the periphery, the number of basal cells decrease progressively more distally, and non-ciliated cells too are unequally distributed. Most airway epithelial cell types such as ciliated cells, clara cells and goblet cells secrete ions, phospholipids, mucus, surfactant, and immunoprotective proteins. The functions of airway mucociliary system are mainly dependent on two events: ciliary beats and ion transport. When these two important parameters are compromised, several untoward consequences such as respiratory infection, obstructive pulmonary pathology

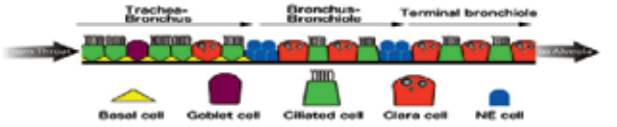

Figure1: Schematic diagram representing expression of various cell types in different region of bronchial epithelial cells.As we move from proximal (trachea) to distal (bronchioles) airways lining, the number of ciliated cells decreases with reciprocal increase in secreting clara cells. No expression of mucus secreting goblet cells found at terminal bronchioles. Source: RIKEN Centre of Developmental Biology, Lung Development Department.

can result in. Thus, the ion and water transport mechanism across the respiratory epithelium is of particular interest for the genesis or therapy of obstructive airway disease like COPD because it plays an essential role in the regulation of the bronchial mucus composition and volume. The PCL together with the mucous layer that covers the PCL forms the airway surface liquid (ASL) as shown in figure 2. ASL is also thought to be regulated by the ion transport processes across the

airway epithelium in a vectorial manner.Transport involves two main ionic movements as shown in figure 3: chloride secretion and sodium absorption by the epithelial cells, associated with parallel movements of water. The ability of respiratory epithelia to secrete chloride depends on CFTR, a cAMP activated apical Cl- channels while ENaC efficiently absorb sodium from PCL. The expression and function of both CFTR and ENaC are correlated to maintain proper osmotic balance required to maintained efficient hydrated state of airway epithelia. Interestingly, apart from CFTR, recent investigation reveals that calcium activated chloride channels (CaCC) also play a significant role in apical Cl- secretion. Thus, apical Cl- secretion from the secretary cells is the cumulative effect of both CFTR and CaCC in respiratory epithelia. Impaired Cl- secretion due to dysfunctional CFTR and/or CaCC affects other channels including ENaC. Furthermore, dysfunctional CFTR cause increase ENaC mediated Na+ absorption and thus results in abnormally high viscous mucus composition of ASL. This hyperviscosity of mucus provides the optimum milieu for pathogenic microbes to colonize in respiratory tract leading to progressive lung inflammation. Therefore, ion channels of these native respiratory epithelia are increasingly being targeted for restoring their normal physiologic function for better control of these pulmonary diseases such as COPD.

Mucous secretion by goblet cells in COPD pathogenesis:

Mucus is a thick viscous liquid that lubricates the airways epithelia and protect the underlining cells from noxious agents and pathogens. Mucin, the main component of mucus, is a high molecular weight glycoprotein secreted by goblet cells. The primary genes involves in airways mucin production are MUC2, MUC4, MUC5AC, and MUC5B. Research in COPD reveals mucus metaplasia or mucus hypersecretion along with increased mucus secreting goblet cell numbers as one of the major patho-physiological features observed in COPD patients. In addition to this, hypertrophy of submucosal glands along with ineffective cough secondary to respiratory muscle weakness and reduced peak expiratory flow are attributed as main reasons for mucus hypersecretion. Etiologies associated with mucus hypersecretion are cigarette smoke exposure, bacterial infections, acute and chronic viral infections, and increased mucin gene expression and mucin synthesis by inflammatory cell activation particularly through EGF (Epidermal Growth Factor) receptor activation. These etiological agents as listed above increase mucin production mainly through stimulation of EGFR signaling cascade resulting in the activation of extracellular-signal regulated kinases (ERK) 1/2 and/or phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3)/AKT signaling pathway. In addition to this, various pro-inflammatory cytokines (IL-9, IL-13 TNF-α, IL-1β) and transcription factors (AP-1 and/or Sp1) act synchronously to increase mucin synthesis to protect against inhaled pathogens. Thus, an alternative approach for treating COPD patients also aims at developing novel drugs that

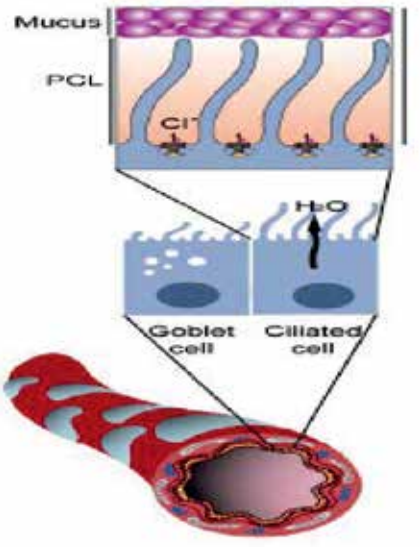

Figure2: Pictorial representation of ASL composed of PCL and mucus in healthy individuals. Source: Am J Physiol Lung Cell MolPhysiol 305: L530–L541, 2013.

specifically suppress these pro-inflammatory signalling molecules activated during COPD pathogenesis.

How a defective ion-transport could lead to thick mucus in the pathogenesis of COPD:

Because of similar symptoms associated with both Cystic Fibrosis (CF) and COPD and that dysfunctional CFTR is a major reason for the

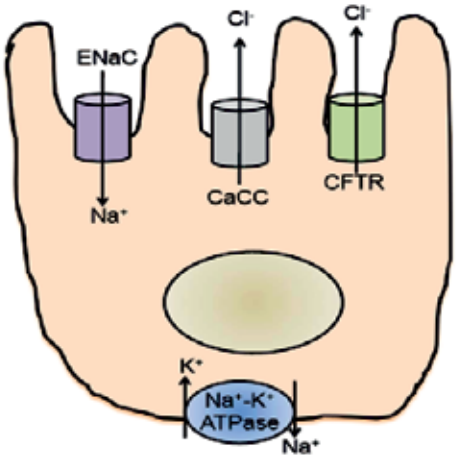

Figure 3: A simplified diagram illustrating major ion channels and transporters involve in maintaining the ionic balance of ASL. CFTR and CaCC are the primary apical Cl- channels that efflux Cl- into the PCL along with Na+ absorbing ENaC in airway epithelia. Basolateral Na+-K+-ATPase provide the necessary electromotive force required for efflux of ions from the apical plasma membrane to the airway lumen.

development of CF, it is tempting to consider Cl- transporting ion channels as a major player in the pathogenesis of COPD.

During pathophysiological conditions as depicted in figure 4, perturbed ion channels function caused reduced ASL height and accumulation of hyperviscous mucus which correlate with inefficient pathogen clearance leading to various bacterial and viral infections and others respiratory protein synthesis. Also CS being highly oxidizing in nature, triggers Reactive Oxygen Species (ROS) formation within these bronchioles and provokes CFTR internalization from the plasma membrane into aggresome-like compartments within the cytosol. The cumulative effect of CS cause functional decrease in CFTR mediated Cl- secretion into the ASL in response to mucin hypersecretion, causing ASL/mucus dehydration and impaired mucus clearance, Thus increasing susceptibility to chronic lung infections. Not only CFTR, Na+ absorbing ENaC also plays an equally significant role in COPD pathogenesis. In healthy individuals, both CFTR and ENaC function synchronously to maintain delicate balance between Cl- secretion and Na+ absorption across the airway which is critical for regulating appropriate height and ionic composition of ASL. ENaC is negatively regulated by CFTR and in COPD patients, the absence of CFTR results in ENaC hyperactivity, leading to abnormally high Na+ absorption and ASL volume

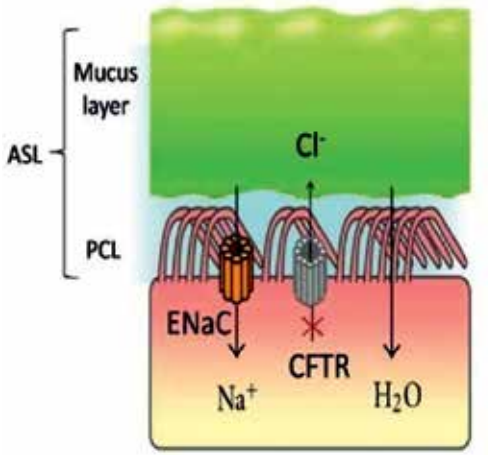

Figure 4:Pictorial representation of impaired ion transport mechanism during COPD pathogenesis. Due to defective CFTR in COPD, Cl– secretion is impaired and Na+ absorption through ENaC is upregulated resulting in dehydration of the ASL with thick mucus accumulation causing PCL to collapse.

depletion or dehydration, leading to compromised mucus clearance and chronic bacterial infections which eventually leads to progressive lung destruction.

Conclusion:

The present review concludes that dysregulated function of ion channels are one of the major contributors of COPD pathogenesis. Hence the present intrinsic strategies for treating COPD aims at restoring the delicate balance between Cl- secretion and Na+ absorption by restituting

CFTR and ENaC function which is required for maintaining the height of ASL in respiratory epithelia. An increasing trend is observed where pharmaceutical companies are targeting these dysfunctional ion channels to ameliorate COPD mainly because of the ease with which these ion channel activity can be modulated by using various ion channels modulators. In this context, High Throughput Screening Technology identified VX-770 as one of the most promising drugs for treating COPD that specifically potentiate CFTR mediated Cl- secretion. A phase 2 clinical trials reveals oral administration of VX-770 increase of the CFTR channel activity in cultured HBE. However, specificity in action, bioavailability within the cells and effective cost are major obstacles associated with these ion channel modulators use in treating COPD patients. More research needs to be done to develop better and novel ways to restore these ion channels functions for effective and potent innate immune response against COPD pathogenesis.

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