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Anoctamin 1 in secretory epithelia

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ABSTRACT

Fluid and electrolyte releasing from secretory epithelia are elaborately regulated by orchestrated activity of ion channels. The activity of chloride channel at the apical membrane decides on the direction and the rate of secretory fluid and electrolyte. Chloride-dependent secretion is conventionally associated with intracellular increases in two second messengers, cAMP and Ca^{2+}, responding to luminal purinergic and basolateral adrenergic or cholinergic stimulation. While it is broadly regarded that cAMP-dependent Cl^- secretion is regulated by cystic fibrosis transmembrane conductance regulator (CFTR), Ca^{2+}-activated Cl^- channel (CaCC) had been veiled for quite some time. Now, Anoctamin 1 (ANO1 or TMEM16A) confers Ca^{2+}-activated Cl^- currents. Ano 1 and its paralogs have been actively investigated for multiple functions underlying Ca^{2+}-activated Cl^- efflux and fluid secretion in a variety of secretory epithelial cells. In this review, we will discuss recent advances in the secretory function and signaling of ANO1 in the secretory epithelia, such as airways, intestines, and salivary glands.

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1. Introduction

Epithelium is a membranous tissue composed of one or more layers of cells that form the cavities or glands of the body. Epithelial cells act multiple functions, such as protection, transportation, absorption, and secretion across the boundary between cavity and surface [1–3]. Secretory epithelial cells release fluids or electrolytes that are necessary for various processes, including in digestion, protection, excretion of waste products, and metabolic regulation [1–3]. The total amount of secretions was drastically adjusted by their rate and direction in response to external stimuli. Chloride flow across the secretory epithelial cells is an important determinant to fluid and electrolyte secretion.

In most non-epithelial cells, the concentration of intracellular Cl^- is close to its electrochemical equilibrium. However, in epithelial cells, $Na^+/K^+/2Cl^-$ co-transporter 1 (NKCC1) located in the basolateral membrane maintains electrochemical Cl^- concentration as high as five-fold in secretory epithelial cells [4–6]. The driving force for Cl^- uptake is provided by the Na^+ gradient which is established by Na^+/H^+-ATPase exchanger. High Cl^- concentration is a key factor for driving Cl^- out to the lumen. Thus, the activation of Cl^- channels induces the Cl^- efflux from apical membrane into the lumen [4–6]. The Cl^- efflux is electrically neutralized by the discharge of K^+ via K^+ channels [4–6]. This luminal accumulation of ions sets a transepithelial osmotic gradient to drive the movement of fluid [4–6]. Thus, the conductance of Cl^- plays an active part in determining the rate and direction at which fluid and electrolyte secretion occurs.

Intracellular cAMP and Ca^{2+} function as second messengers to regulate chloride-dependent secretion [5]. cAMP-activated Cl^- currents are mainly mediated by CFTR, an anion channel that belongs to ATP-binding cassette transporter gene family. In secretory epithelial cells, cAMP-activated CFTR is localized in the apical membrane, and its dysfunction in cystic fibrosis severely impairs the luminal fluid and composition [7]. Although CFTR is clearly related with fluid and electrolyte secretion in secretary epithelia, Cl^- dependent secretion is still observed in the epithelia cells isolated from patients with cystic fibrosis and mice lacking *Cftr* [8,9]. This 'remnant' secretion appears to be mediated by intracellular Ca^{2+} [8,9]. In fact, the increase in intracellular Ca^{2+} using direct application of Ca^{2+} ionophore and the activation of purinergic receptors evokes Ca^{2+}-activated Cl^- currents in both normal and cystic fibrosis originated airway epithelial cells [10,11]. These Ca^{2+}-activated Cl^- currents are voltage dependent and inhibited by some Cl^- channel blockers such as DIDS, niflumic acid, and NPPB [5,7,12]. The single channel conductance typically showed 1–15 pS in secretary epithelial cells, and have an anion selectivity sequence of $I^- > NO_3^- > Br^- > Cl^-$ [5,7,12,13].

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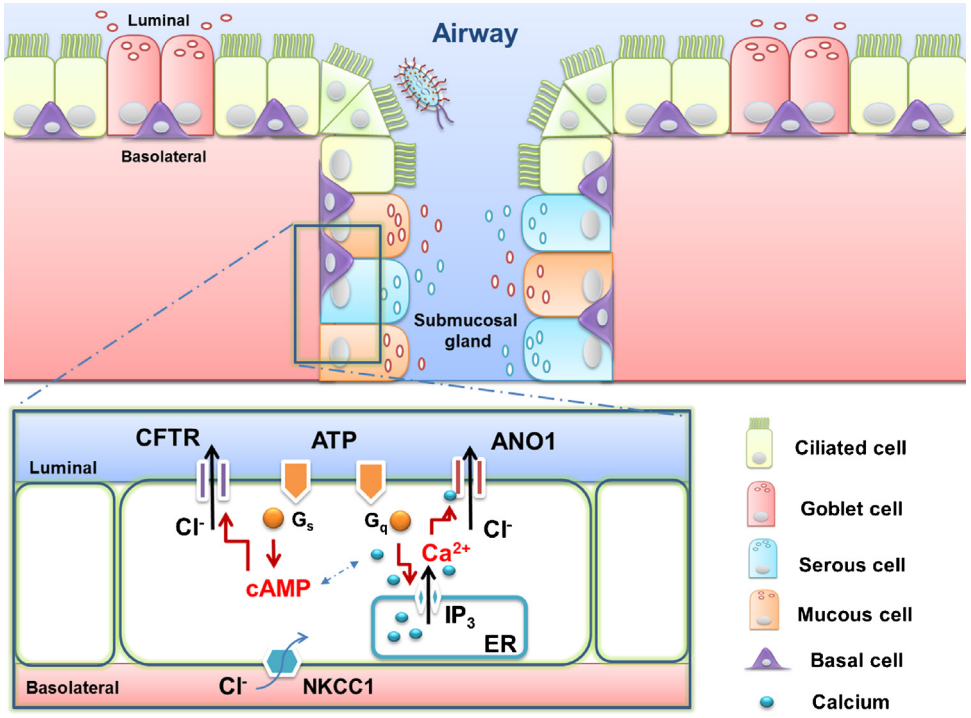

Fig. 1. The ANO1-mediated secretary signaling in the airway. The stimulation of luminal purinergic receptors causes an increase in intracellular cAMP and Ca^{2+}. cAMP induces Cl^- secretion through the activation of CFTR in the luminal side whereas intracellular Ca^{2+} causes Cl^- secretion through the activation of ANO1. Occasionally, a cellular crosstalk between CFTR and ANO1-dependent secretions regulates the secretory signaling in the airway epithelia.

Undiscovered for quite long time, CaCC was finally cloned. Yang et al. reported that TMEM16A confers CaCC currents. They renamed it as anoctamin 1 (ANO1) because it is an anion channel with octa-(8) transmembrane domains [14]. Coincidently, independent two other groups also reported that TMEM16A acts as a CaCC [15,16]. Because ANO1 shows similar biophysical property, pharmacological profile as well as expression pattern with those of CaCCs, it is now generally accepted that ANO1 is a candidate gene for CaCC. In this review, we will address recent advances in studying ANO1 in the secretory epithelial cells.

2. Cl^- channels in airway epithelium

The airway epithelium serves a dynamic host barrier designed to protect from toxic and infectious materials in inhaled air. Besides the physical barrier of epithelial cells, their viscoelastic resistance exerted effectively by the airway surface layer (ASL) has a protection from pathogens. ASL is composed of soft elastic solid and viscous fluid secreted by airway epithelial cells. Due to their viscous nature, penetrated pathogens are trapped and removed from the lung through ciliary beatings and coughs.

According to unique morphology and functions, airway epithelial cells are broadly separated into basal, secretory and ciliated epithelial cells (Fig. 1). The basal cells are populated beneath secretory and/or ciliated cells and attached on the top of the basement membrane, which helps to anchor the epithelium to the matrix. Moreover, basal cells have been reported to possess stem cell like properties so that they can differentiate into secretory or ciliated cells after epithelial injury [17]. While basal cells have a role in connecting and supporting other epithelial cells, secretory and ciliated cells take part in the formation and regulation of ASL to trap and remove pathogens. The secretory cells are further divided into subtypes such as goblet (or mucous) and serous cells, which predominantly produce mucin proteins that impart the properties of sticky gel in the airway. Besides mucin proteins, these secretory cells have been known to secrete a variety of antimicrobial peptides (β-defensin and lysozymes), immunomodulatory molecules (chemokines and cytokines), and protective molecules such as growth factors into mucus [18–21].

The viscoelastic mucus layer containing ASL is composed of water, proteins (mainly mucins), salts, and lipids, which is generally maintained in 97% solvent and 3% solids in the normal mucus layer [1]. This mucous property is maintained by well controlled secretion of electrolytes and water. Electrolyte secretion is associated with Cl^- secretion through CFTR and CaCCs in airway epithelial cells.

The stimulation of luminal purinergic receptors causes increase in intracellular cAMP and Ca^{2+}, which induces cAMP- or Ca^{2+}-dependent Cl^- secretion out of epithelial cells and consequently regulates the quantity and composition of the respiratory tract fluid [22]. CFTR mediates the cAMP-dependent Cl^- secretion, which is genetically defective in the patients with cystic fibrosis [7]. Besides the Cl^- channel function, it can also modulate the activity of other transporters such as ENaC in a cAMP dependent fashion [23]. The cAMP-mediated protein kinase A (PKA) regulates cAMP-mediated trafficking and activation of CFTR [24]. Indeed, forskolin, a cAMP inducer, shows a considerable reduction in the tracheas of CFTR deficient mice whereas there is no difference in response to purinergic receptor agonists compared to wild-type mice [25].

Although Cl^- secretion in the cystic fibrosis was reduced by the dysfunction of CFTR, other Cl^- secretion such as via CaCC is still remained to be determined [8,9]. The second messenger, intracellular Ca^{2+}, is an important regulator for fluid secretion. In fact, the application of Ca^{2+} ionophore and the activation of purinergic receptors evoke Ca^{2+}-activated Cl^- currents in both normal and cystic-fibrosis originated airway epithelial cells [10,11].

3. ANO1 as a candidate for CaCC

In search of a CaCC candidate gene, many genes such as CLCA, ClCs, Tweety, and bestrophins were introduced [26]. However, none of them satisfied the hallmark property of CaCC. CaCCs are

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