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Ion Transporting Proteins of Human Bronchial Epithelium

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ABSTRACT

The electrolyte transport system across human airway epithelium followed by water movement is essential for the normal mucociliary clearance that allows the maintenance of the aseptic condition of the respiratory tract. The function of epithelial cells is to control and regulate ionic composition and volume of fluids in the airways. Various types of proteins taking part in assuring effective ions and water transport in apical and basolateral membranes of the airway epithelium have been found (e.g., CFTR, ENaC, CaCC, ORCC, potassium channels, NaKATPase, aquaporins). The paper reviews the current state of the art in the field of ion channels, transporters, and other signaling proteins identified in the human bronchial epithelium. J. Cell. Biochem. 113: 426–432, 2012.

KEY WORDS: BRONCHIAL EPITHELIUM; ION CHANNELS AND TRANSPORTERS; CYSTIC FIBROSIS; ACTIVATORS AND INHIBITORS OF ION CHANNELS

Airway epithelium acts as a high electric resistance barrier that separates luminal from the interstitial compartments. In the lower airways, bronchial epithelium is involved in a chemical and physical defense allowing for detoxification and trapping of inhaled particles and then transporting them to the oropharynx. Airway epithelium is covered with a thin layer of fluid called airway surface layer (ASL) composed of periciliary liquid layer (PCL), and mucus phase (Fig. 1). Inhaled particles are transported by cilia and trapped by mucus, so that synergistic effect of mucus, periciliary layer, and cilia provides pulmonary defense mechanism. The effective beating of cilia is dependent on the proper depth of PCL; thus, maintaining the proper ionic composition and volume of PCL is crucial for the efficient mucociliary transport. Regulation of PCL volume and composition is intrinsically related to epithelial ion transport carried by the ion transporting proteins of the airway epithelium. Up to now over 100 ion channels, pumps, transporters and receptors have been identified in the human airway epithelium (the most recognized transporting proteins are shown in Fig. 1). They create a kind of network where particular element can influence many others. For example, CFTR channel was found to influence ENaC, ORCC, VSOR channels or even sodium-potassium pump. The paper presents current knowledge and recent findings on the proteins involved in transport in the human bronchial epithelium.

CHLORIDE CHANNELS

CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR (CFTR)

Due to a great importance in lethal genetic disease—cystic fibrosis (CF), CFTR is the most intensively studied chloride channel of the human airway epithelium (Proesmans et al., 2008). Broad investigations of CFTR allowed for obtaining detailed characteristics of this channel. CFTR is apically localized member of the ATPase-binding cassette (ABC) transporter family and unlike other members of this family, it has the ability to conduct chloride as well as bicarbonate anions with selectivity ratio $Cl:HCO_3 = 4:1$ (Kim and Steward, 2009). CFTR is activated by cAMP and protein kinase A (PKA), Ca^{2+}-dependent protein kinase C (PKC), cyclic guanosine monophosphate-dependent kinase (PKG), and stimulation of G proteins. It requires binding of two ATP molecules to open and hydrolysis of one of them to close (Hwang and Sheppard, 2009). CFTR channel consists of two repeated motifs made up of six transmembrane domains (TMD1 and TMD2), two cytoplasmic nucleotide binding domains (NBD1 and NBD2) and one regulatory domain (R). The two transmembrane domains form a pore through which ions flow across the membrane. The pore is closed by the R domain in its unphosphorylated state. It was found that the residues in TMD1 played the most important role for the CFTR in terms of

Abbreviations: DIDS, 4′-diisothiocyano-2,2′-stilbenedisulfonic acid; DTT, dithiothreitol; NPPB, 5-nitro-2-(3-phenylpropylamino)benzoic acid; ChTx, charybdotoxin; DNDS, 4,4′-dinitrostilben-2,2′-disulfonic acid; 1-EBIO, 1-ethyl-2-benzimidazolinone.

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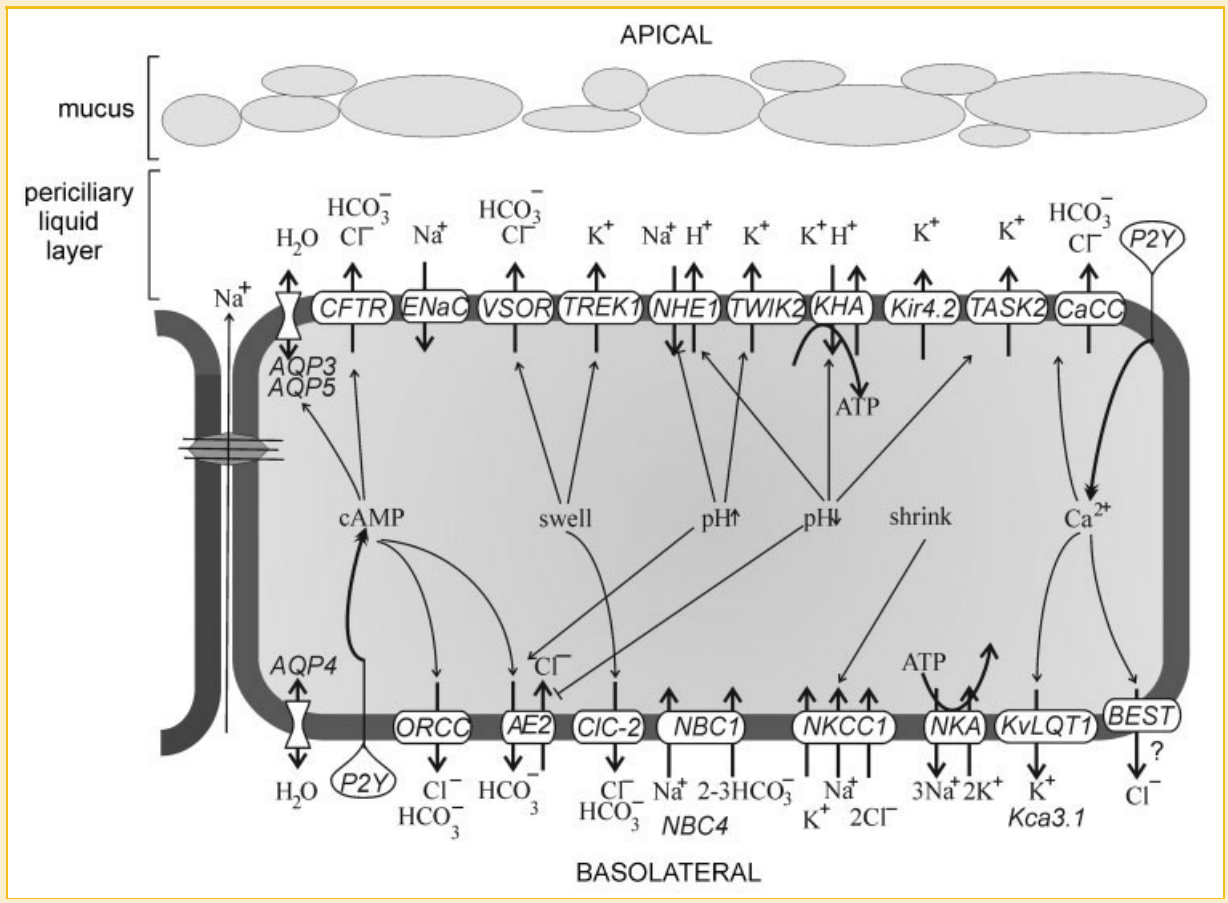

Fig. 1. Schematic presentation of the human bronchial epithelium structure and its transporting proteins.

selectivity, conductance, and channel open probability, while TMD2 of CFTR may be involved in maintaining stability of the channel in the open state. Electrophysiological studies of CFTR showed that the channel had a linear, nonrectifying I/V relationship and single-channel conductance of approximately 9–11 pS (Cai et al., 2006). For pharmacological activators and inhibitors of CFTR channel, see Table I.

CALCIUM ACTIVATED CHLORIDE CHANNEL (CaCC)

CaCC (also named CLCA) is the apical channel of the human bronchial epithelium found by short-circuit measurements or whole-cell patch clamp (Gabriel et al., 2000). Molecular identity of CaCC is still controversial due to the problems with cloning of the channel and the lack of sufficiently selective blockers and antibodies against CaCC. In spite of these problems, structure of CaCC (CLCA

TABLE I. Activators and Inhibitors of Transport Proteins in Apical Membrane of the Human Bronchial Epithelium.

Name	Gene	Activator	Inhibitor
K^+ channels			
TREK-1	kcnk2	halothane, chloroform, isoflurane, arachidonic acid	lidocaine, quinidine, Gd^{3+}, fluoxetine bupivicaine
TWIK-1	kcnk1	PMA	quinidine, Ba^{2+}
TWIK-2	kcnk6	arachidonic acid	halothane
TASK-2	kcnk5	halothane	bupivacaine, quinine, quinidine, acidic pH, lidocaine, clofilium
Kir4.2	kvnj15	ATP	Ba^{2+}
Cl^- channels			
CFTR	cftr	ATP, forskolin, genistein, phloxine, apigenin	glibenclamide, arachidonic acid, ibuprofen
CaCC (CLCA)	clca1 clca2 tmem16a	ionomycin, >2 mM Ca^{2+}, norepinephrine, ATP, endothelin	niflumic acid, DIDS, DTT
VSOR	not known	H_2O_2	glibenclamide, DIDS, NPPB, niflumic acid, Mg^{2+},verapamil
Na^+ channels			
ENaC	enac	aldosterone, insulin, vasopressin	amiloride, triamterene, benzamil
Ion transporters			
Na/H ion exchanger	nhe1	acidic pH	angiotensin II, amiloride
HKATPase	atp1al1	histamine	ouabain, oligomycin, SCH28080

protein) was elaborated by a few groups. It was proposed that CaCC might be composed of five transmembrane domains cleaved in a NH_2-termining fragment containing membrane spanning domains 1–3 and a COOH-terminal fragment with two transmembrane domains. CaCC conductance varies from 4 to 8 pS and exhibits outward rectification for ($Ca^{2+} < 1\ \mu M$) and linear current-voltage relationship for higher Ca^{2+} concentrations (Wei et al., 1999). CaCC poorly discriminates between anions (e.g., $I^- > Cl^-$) and its anion permeability sequence is consistent with Eisenmann I sequence. Activators and inhibitors of CaCC channel were presented in Table I.

VOLUME SENSITIVE OUTWARDLY RECTIFYING CHLORIDE CHANNEL (VSOR)

VSOR channel is considered to be the cell volume sensor, since it is mainly activated by osmotic swelling (Okada et al., 2009). Its presence in the human bronchial epithelium was shown by Ussing chamber measurements and whole-cell patch clamp. VSOR exhibits unitary conductance of 50–70 pS, high open probability >0.95, moderate outward rectification, and high positive potential of inactivation. VSOR shows $I^- > Br^- > Cl^- > F^-$ permeability sequence in human epithelial cells. Its channel activity requires direct binding of intracellular ATP to the channel protein. VSOR plays a role in maintaining intracellular acid–base equilibrium through permeability of lactate and bicarbonate ions. Recent studies suggest that VSOR plays many other functions like regulation of cell proliferation, induction of apoptotic cell shrinkage, or counteracting necrotic cell swelling (Okada et al., 2006). VSOR is thought to mediate release of large anions like ATP. Its activity is blocked by glibenclamide (for more details see Table I). Despite well-characterized properties and great importance of VSOR channel in many biochemical processes, its molecular identity is still not known.

BESTROPHINS

Basolaterally localized bestrophins are molecular candidates for calcium activated chloride channels having linear I/V relationship (Hartzell et al., 2008). The other standpoint states that bestrophins are not chloride channels but rather channel regulators, e.g., they were found to regulate voltage-gated Ca^{2+} channels (Duta et al., 2004; Marmorstein et al., 2006). They are encoded by *Best*1-4 genes. hBest1 is regulated by intracellular Ca^{2+}, cell volume and inhibited by hyperosmotic solution (Duta et al., 2006). Current models of bestrophin structure suggest this protein consists of either four or six transmembrane spanning α-helices and C-terminal cytoplasmic region. Bestrophins are regulated via cAMP- and cGMP-dependent pathways. For the pharmacological activators and inhibitors, see Table II.

CLC-2 CHANNEL

ClC-2 channel belongs to CLC gene family of chloride channels. This type of channels was thought to have 10 or 12 transmembrane domains, but recently, it has been reported that CLC channels are supposed to be homodimers in which each monomer has only one pore. It exhibits conductance as low as 2–3 pS (Jentsch et al., 2002). CLC-2 is localized on basolateral face of the epithelial cell. The channel is activated by hyperpolarization, cell swelling, and acidic pH (Table II). It takes part in pH and cell volume regulation (Dutzler et al., 2002).

OUTWARDLY RECTIFYING CHLORIDE CHANNEL (ORCC)

Before CFTR was cloned, outwardly rectifying chloride channel had been recognized to be the primary defect in CF. ORCC had been thought to be present in apical membrane of bronchial epithelium. However, single-channel patch clamp studies of Calu-3 cells suggested that ORCC could be localized in basolateral membrane (Hwang et al., 2000; Szkotak et al., 2003). It was shown that ORCC is activated by cAMP in wild but not in CF airway epithelia (Kreindler, 2010). However, ORCC is activated by ATP in both wild and CF cells. It exhibits the conductance of 30–70 pS, a rectifying I/V relationship and is activated with depolarizing voltages. ORCC was found to be sensitive to DIDS and to be halide permselective ($I^- > Cl^-$) (Table II).

SODIUM CHANNELS

EPITHELIAL SODIUM CHANNEL (ENaC)

The apical sodium channel ENaC allows for transcellular transport of Na^+ ions. The channel is also thought to play an important role in cell volume regulation (Caci et al., 2009). ENaC channel plays crucial

TABLE II. Activators and Inhibitors of Transport Proteins in Basolateral Membrane of the Human Bronchial Epithelium

Name	Gene	Activator	Inhibitor
K^+ channels			
KvLQT1	kcnq1	cAMP, Ca^{2+}, 1-EBIO	chromanol compound 293B, clofilium, linopirdine, Ba^{2+}
hIK-1 (hSK4, KCa3.1)	kcnn4	1-EBIO, Ca^{2+}, 7,8-benzoquinoline	clotrimazolum, ChTx, Ba^{2+}
Cl^- channels			
ORCC	not known	cAMP Gd^{3+}	DIDS
ClC-2	clc-2	acidic pH, lubiprostone, arachidonic acid, omeprazole	Zn^{2+}
bestrophins	best1	NO, ATP, ionomycin	DIDS, niflumic acid
Ion transporters			
Na2HCO3 ion transporter	nbc1, nbc4	forskolin, calmodulin, carbachol	DIDS, DNDS
NaK2Cl ion transporter	nkcc1	ATP, pinacidil	bumetanide, furosemide, benzmetanide, torsemide
Cl/HCO3 ion exchanger	ae2	NH_4^+	calmidazolium, acidic pH, DNDS, DIDS
NaKATPase (NKA, EC 3.6.1.3)	atp1q1, atp1a2	thyrotropin, aldosterone	β –mercaptoetha-nol, vanadate, DTT, ouabain, oligomycin, 3,4,5,6-tetrahydroxy-xanthone, oleandrin, digoxin

role in Na^+ and water homeostasis. ENaC is permeable for Li^+, H^+, and especially for Na^+ (Na^+/K^+ selectivity ratio was estimated to be >500). It is arguably the most selective ion channel and is indicated by single-channel conductivity of 4–5 pS. ENaC discrimination among cations is based on their size (larger cations such as K^+, NH_4^+ cannot pass through the channel). That is why ENaC interacts only with monovalent cations. Subunit stoichiometry of ENaC can be assessed by expression of trimeric or tetrameric subunits α, β, and γ linked in a head-to-tail fashion (Gaillard et al., 2010). Its subunit contains intracellular N- and C-termini, two transmembrane domains, and a large extracellular loop. ENaC subunits belong to the degenerin/ENaC family of ion channels. Their characteristic feature is the presence of short intracellular domains, two transmembrane spanning domains, and large extracellular domains containing multiple cysteine-rich domains. The ENaC pore progressively narrows down to a binding site that accepts small inorganic cations and finally to the narrowest port of the pore, the selectivity filter that accommodates exclusively the permeating Li^+, H^+, and Na^+ ions. For the activators and inhibitors of ENaC, see Table I.

POTASSIUM CHANNELS

VOLTAGE-DEPENDENT POTASSIUM CHANNELS (K_v), CALCIUM-ACTIVATED POTASSIUM CHANNELS (K_{Ca}) TWO PORE-DOMAIN POTASSIUM CHANNELS(K_{2P}), INWARD-RECTIFYING POTASSIUM CHANNELS (K_{ir})

In human bronchial epithelium there have been identified more than 30 potassium channels of three main K^+ channel groups: Six transmembrane domain (K_v and K_{Ca} channels), four transmembrane domain (K_{2P} channels), and two transmembrane domain-channels (K_{ir} channels) (Bardou et al., 2009a).

Voltage-gated potassium channels of basolateral membrane consist of six membrane-spanning segments with cytoplasmic N- and C-terminal domains. The S4 membrane-spanning segment contains a positively charged amino acid at every third position that serves as the transmembrane voltage sensor for voltage-dependent gating. The pore region, formed by S5 and S6 segments and as intervening loop, is responsible for K^+ ion conduction and K^+- selectivity. Among 6-TMD channels, KvLQT1 (Kv7.1, KCNQ1) has been the most intensively studied. It belongs to 6-TMD group and it opens by membrane depolarization (Jespersen et al., 2005). The channel exhibits conductance <3 pS and its presence at the basolateral membrane was shown by the immunofluorescence method and Ussing chamber measurements (Table II). Apart from KvLQT1 channel, other K_v channels have been identified in the human bronchial epithelium usually on the basis of PCR results alone. mRNA transcripts of Kv channels: Kv1.5 (KCNA5), Kv1.7 (KCNA7), Kv6.1 (KCNG1), Kv7.2 (KCNQ2), Kv7.3 (KCNQ3), Kv7.4 (KCNQ4), Kv7.5 (KCNQ5) have been found. Other than K_v, six transmembrane domain channel identified in the human bronchial epithelium is K_{Ca} channel: KCa3.1 (hIK-1, SK4) (Wilson et al., 2006; Moser et al., 2008; Bardou et al., 2009b). The presence of hIK-1 channel has been shown by Ussing chamber measurement and patch clamp studies with transfected cells. The conductance of the channel was estimated on about 33 pS.

K_{2P} channels were found in apical membrane (Enyedi and Czirjak, 2009). They are built of four transmembrane domains (M1–M4) and two pore regions called P1 and P2 inserted into the membrane from the outside. In airway epithelial cells there are TREK-1 (KCNK2), TWIK-1 (KCNK1), TWIK-2 (KCNK6), and TASK-2 (KCNK5) channels. TREK-1 is an outwardly rectifying channel, opened by membrane stretch, cell swelling, and shear stress (Xian et al., 2006). The conductance of TREK-1 ranges from 95 to130 pS at positive voltages. The channel's conductance is reduced by extracellular Mg^{2+} and Ca^{2+}. For activators and inhibitors see Table I. TWIK-2 is a weakly inwardly rectifying K^+ channel whose activity is influenced by the membrane potential and which is inhibited by cytoplasmic acidification. TASK-2 is a twik-related alkaline pH-activated potassium channel, highly sensitive to pH changes, having single-channel conductance of 60–70 pS in symmetrical K^+ solution (Kang and Kim, 2004). Its inward rectification depends on the presence of intracellular Na^+. In the group of apical two-transmembrane-domain channels of the bronchial epithelial cells, mRNA transcripts for Kir 1.1 (ROMK1) and Kir 4.2 (Kir 1.3) channels were found, but only Kir4.2 channel's presence was proved by means other than PCR technique. Its single-channel conductance was estimated on ~24 pS by single-channel patch clamp method (Wu et al., 2004).

WATER CHANNELS: AQUAPORINS

Aquaporins are the family of water channels involved in epithelial transport (Agre et al., 2002). There are 11 aquaporin-type mammalian proteins of which four are expressed in the human bronchial epithelium: AQP1, AQP4, AQP5 (permeated only by water), and AQP3 (permeated by water and other small solutes, e.g., glycerol) (Tradtrantip et al., 2009). Aquaporin water channels consist of six membrane-spanning segments arranged in two hemi-pores forming hourglass-shaped channel. The channel narrows to a diameter which physically limits the size of molecules than can pass through. Additionally, a specific motif in aquaporin structure is the three-amino-acid sequence NPA (asparagine–proline–alanine). Orientation of a pair of dipoles at the NPA motif is crucial for channel permeability (Agre, 2006). Dipoles at the NPA interact with a single water molecule and prevent it from hydrogen bonding with other water molecules what eliminates the posibility of H^+ ions transfer through the channel. Thus, the combination of size and charge restrictions allows for the controlled permeability of water channels (Fu and Lu, 2007). AQP5 was identified at apical and AQP4 at basolateral membrane of human airway epithelium. Localization of other AQPs is still not clear. Aquaporins are inhibited by 0.3 mM $HgCl_2$ with the exception for AQP4.

ION TRANSPORTERS

In contrary to ion channels where ions move by passive transport, in the airway epithelium there are also membrane transport proteins that move ions against their concentration gradient,

descripted as ions transporters. Among them we can distinguish between ion pumps: NaKATPase and HKATP-ase, cotransporters: NaK2Cl and Na2HCO_3, and antiporters (ion exchangers): Na/H and Cl/HCO_3.

Basolateral NaK2Cl belongs to the family of Cl^- dependent cation transporters (NKCCs). It mediates the coupled electroneutral transport of $1Na^+$, $1K^+$, and $2Cl^-$ across the plasma membrane, driven by the inwardly directed Na^+ gradient that occurs under physiological conditions. Two isoforms of NKCC have been identified, NKCC1 and NKCC2 (Gillie et al., 2001). NKCC1 is the isoform widely distributed in the airway epithelium. It is activated by cell shrinkage and its major function is regulation of cell volume (Table II). Basolateral sodium-bicarbonate transporters NBC belong to the SLC4 family genes (Cordat and Casey, 2009). They mediate cotransport of Na^+ and HCO_3^- (Pushkin and Kurtz, 2005). Two isoforms NBC1 and NBC4 were found in basolateral membrane of the human bronchial epithelium (Kreindler et al., 2006). In contrary to other SLC4 family members, NBC1 and NBC4 are electrogenic transporters. NBC4 is suggested to have the transport stoichiometry 3 HCO_3^- to 1 Na^+ while NBC1 is reported to have stoichiometry 3:1 or 2:1 (Gross and Kurtz, 2002). For NBC activators and inhibitors, see Table II. Basolateral electroneutral Cl/HCO_3^- exchanger (AE) also belongs to the SLC4 family genes (Table II). It mediates sodium independent Cl/HCO_3^- ion exchange (Shin et al., 2007). In the bronchial epithelium AE2 form has been identified. Apical Na/H exchanger exists in the bronchial epithelium in isoform NHE1 (Table I). The regulatory domain modulates transport activity, probably by altering affinity of H^+ transport site in the transmembrane domain (Putney et al., 2002). Na/H exchanger, like NKCC cotransporter, is thought to play a role in cell volume and pH regulation. It is also involved in cell adhesion, cell migration, and cell proliferation.

Localized at the basolateral membrane, sodium pump (NaKATP-ase, NKA) exports three sodium ions in exchange for two potassium ions against the concentration gradients using the energy from ATP (Wuytack, 2009). The stoichiometry of the reaction is three Na^+ ions transported out of the cell and two K^+ ions into the cell for each hydrolyzed ATP. The sodium pump is called ATPase or NKA because it is membrane-bound ATP-hydrolyzing enzyme system. It has been shown that NKA is composed of two subunits: α, responsible for the catalytic activity of the enzyme, composed of 10 transmembrane domains with five extracellular loops and β, folding the complex, having single membrane crossing and amino terminus in the cytoplasm. Four different isoforms of the two subunits were identified, but in the human airways α1 and α2 subunits were reported. Non-gastric isoform of HKATPase was identified in apical membrane of the bronchial epithelium by immunocyto-chemistry. In contrary to NKA, HKATPase bears no own β subunit and it has been assumed to exploit the β subunit of NKA (Dunbar and Caplan, 2001). Non-gastric HKATPase transport is electro-neutral, though inward transport of K^+ is much more abundant than outward transport of H^+ what led to the idea that Na^+ is also transported by non-gastric HKATPase (Swarts et al., 2005, 2007). For activators and inhibitors of NaKATPase and non-gastric HKATPase, see Tables I and II.

PURINERGIC RECEPTORS

Purinergic receptors (purinoreceptors) P1 (adenosine receptors) and P2Y receptors have been found in both apical and basolateral membranes of the human bronchial epithelium. There are A_1, A_{2A}, A_{2B}, and A_3 subtypes activated by adenosine, but the best confirmed in the human airways is A_{2B} receptor at the apical surface (Com and Clancy, 2009). Among metabotropic P2Y family, $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$ receptors were identified in the human airway epithelium (Wong et al., 2009). Members of P2Y group show significant differences in their pharmacological profiles, e.g., some are activated by nucleoside diphosphates ($P2Y_1$, $P2Y_6$), while others are activated by nucleoside triphosphates ($P2Y_2$, $P2Y_4$). Some P2Y receptors are activated by both purine and pyrimidine nucleotides ($P2Y_4$, $P2Y_4$, $P2Y_6$) and others by purine nucleotides alone, like $P2Y_1$ receptor. The predominant receptor in the bronchial epithelium is $P2Y_2$. It is coupled to PLC and Ca^{2+} signaling cascade what enables increase in intracellular calcium concentration by ATP and UTP. Thus, stimulation of $P2Y_2$ activates Ca^{2+}-dependent secretion and inhibits Na^+ reabsorption. Functional expression of other purinor-eceptors in airway remains controversial. However, A_{2B}, $P2Y_1$, $P2Y_2$, $P2Y_6$ receptors were found to be stimulating factors of CFTR channel activity (Marcet and Boeynaems, 2006; Faria et al., 2009). The physiological agonists of the cloned human P2Y receptor are ADP ($P2Y_1$), UTP/ATP ($P2Y_2$), UDP ($P2Y_6$). A_{2B} receptor was found to be stimulated by N-ethylcarboxamidoadenosine, while alloxazine is its antagonist.

SUMMARY

Ion transporting proteins of the human bronchial epithelium are the subject of investigation in many different groups. Despite great efforts, the mechanism of ion and water transport considering all transporting proteins is still not possible to elaborate. It is caused by the complex relationships between transporting proteins in the epithelium. Moreover, new transporting proteins engaged in ion transport are being constantly reported. CFTR, being the best known among all transporting proteins of the human airway epithelium, is a good example how tangled mutual interactions of transporting proteins can be. Numerous studies in the recent years have shown that CFTR interacts with many other channels, transporters, receptors, or other signaling molecules. The best confirmed is down-regulation of ENaC by CFTR though the detailed mechanisms of their interactions are yet not understood (Berdiev et al., 2009). CFTR was also reported to alter CaCC channel. Moreover, CFTR was found to activate Na^+/H^+ and HCO_3^-/Cl^- exchangers, KvLQT1 channel, or even sodium-potassium pump. In 1995 mechanism of regulating basolateral ORCC by CFTR had been published and 4 years later, CFTR, when stimulated by PKA, was found to activate AQP3 what resulted in coupled Cl^- and water transport. Defective CFTR activity causes the CF syndrome, characterized by enhanced Na^+ absorption and failure to secrete Cl^- what leads to ASL volume depletion and defective mucociliary clearance. As CFTR influences other transporting proteins, its mutations are the reason for defected global ion and water transport. Lately, CFTR activity has

been reported to be influenced by P2Y and A_{2B} receptors (Lazarowski and Boucher, 2009). In detail, activation of CFTR by A_{2B} receptor was also investigated by Rollins et al. (2008). Additionally, apical A_{2B} receptors were also found to regulate anion secretion through stimulation of basolateral K_{Ca} channels via PLC/Ca^{2+} signaling. It is also suspected that A_{2B} receptors may activate other than K_{Ca} basolateral potassium channels and also induce mixed secretion of chloride and bicarbonate as a result of its dual regulation of CFTR and K_{Ca} channels. The CFTR channel example shows how complex particular protein interaction with many others proteins can be. This is why detailed knowledge on the transporting proteins in the bronchial epithelium is so important for elaborating reliable mechanism of ionic transport. Knowledge of those mechanisms is indispensable for finding efficient treatment of human airway epithelium diseases connected with disturbed ionic transport like CF.

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