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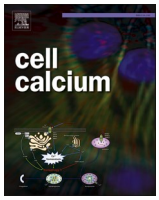

Epithelial Anoctamins

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ABSTRACT

When activated by increase in intracellular Ca^{2+}, anoctamins (TMEM16 proteins) operate as phospholipid scramblases and as ion channels. Anoctamin 1 (ANO1) is the Ca^{2+}-activated epithelial anion-selective channel that is coexpressed together with the abundant scramblase ANO6 and additional intracellular anoctamins. In salivary and pancreatic glands, ANO1 is tightly packed in the apical membrane and secretes Cl^-. Epithelia of airways and gut use cystic fibrosis transmembrane conductance regulator (CFTR) as an apical Cl^- exit pathway while ANO1 supports Cl^- secretion mainly by facilitating activation of luminal CFTR and basolateral K^+ channels. Under healthy conditions ANO1 modulates intracellular Ca^{2+} signals by tethering the endoplasmic reticulum, and except of glands its direct secretory contribution as Cl^- channel might be small, compared to CFTR. In the kidneys ANO1 supports proximal tubular acid secretion and protein reabsorption and probably helps to excrete HCO_3^- in the collecting duct epithelium. However, under pathological conditions as in polycystic kidney disease, ANO1 is strongly upregulated and may cause enhanced proliferation and cyst growth. Under pathological condition, ANO1 and ANO6 are upregulated and operate as secretory channel/phospholipid scramblases, partly by supporting Ca^{2+}-dependent processes. Much less is known about the role of other epithelial anoctamins whose potential functions are discussed in this review.

1. Introduction

Anoctamins (TMEM16 proteins) represent a family of Ca^{2+} activated transmembrane proteins, which operate as ion channels and/or phospholipid (PL) scramblases [1–4]. Except for the anion selective channels ANO1 and ANO2, most anoctamins operate as phospholipid scramblases [5–7], which also conduct ions in a nonselective manner [8–10]. ANO1, ANO2, and ANO6 are found in the plasma membrane, while all other anoctamins are expressed primarily in intracellular compartments [11]. Several anoctamins are expressed in epithelial tissues, but ANO1 is the archetypical epithelial anoctamin due to its anion selectivity and its role in epithelial Cl^- transport in various glands, airways and intestine [12] (https://www.proteinatlas.org/ENSG00000131620-ANO1/tissue).
Gating of ANO1 by an increase in cytosolic Ca^{2+} strongly depends on the membrane voltage and, in addition, is stabilized by plasma membrane phospholipids (PIP_2; cholesterol), cytoskeletal interactions and temperature [13–19]. Regulation by calmodulin and phosphorylation/dephosphorylation by calmodulin-dependent kinase (CAMKII)/protein phosphatase (PPI, PPIIA) has been a matter of controversy and was discussed recently [20–23]. The calcium-activated chloride channel regulator 1 (CLCA1) is also a major regulator of ANO1 that stabilizes expression of ANO1 in the plasma membrane through mechanisms that are not fully understood. CLCA1 is a secreted metalloproteinase that may bind to ANO1 from the extracellular side and possibly dimerizes ANO1 channels in a non-proteolytic way [24] (Fig. 1).

The PL scramblase ANO6 is also abundant in epithelial tissues and is expressed in all cell types [12]. Located primarily in the plasma membrane (PM) it also operates as a Ca^{2+} dependent Cl^- channel (CaCC) or as nonselective large conductance channel (ongoing stimulation) and it requires high intracellular Ca^{2+} concentrations to be activated [8, 25-29]. It is therefore unlikely to contribute directly to epithelial Cl^- secretion, but possibly indirectly by regulating the abundance of ion channels in the PM. However, knockout of ANO6 did not inhibit Ca^{2+}- or cAMP-activated Cl^- secretion in mouse airways or intestine [30,31]. higher temperatures and PM phospholipids increase Ca^{2+} sensitivity, accelerate activation and magnitude of ANO6 and ANO1 currents [15, 32]. Moreover, ANO6 was shown to contribute to secretory diarrhea induced by Vibrio cholerae accessory enterotoxin in a phosphatidylinositol 4,5-bisphosphate (PIP_2) dependent manner [33]. A direct regulation of both ANO6 and ANO1 by PIP_2 was shown in other studies [16, 34-38]. ANO6 also participates in cellular volume regulation and cell

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death, which may be particularly relevant in epithelial tissues which endure large changes in intracellular ion concentrations [33,39-43]. Because of their bidirectional regulatory relationship to membrane lipids and their role in vesicular transport, i.e. membrane insertion of proteins, it is difficult to unravel the contribution of individual anoctamins to epithelial functions, especially since several anoctamin paralogues are expressed in epithelia [31,44-46]. The epithelial function of so-called intracellular anoctamins such as ANO3, 5, 7, 8, 9 and 10 is only slowly appearing and is reviewed in more detail in [11] of this special issue of *Cell Calcium*. They seem to affect Ca^{2+} dependent regulation of epithelial Cl^- transport, which is discussed below for individual epithelial tissues.

2. Brain and eye

The choroid plexus (CP) present in the brain ventricular system produces the cerebrospinal fluid (CSF). ANO1 is located in the apical membrane of CP epithelial cells and contributes to secretion of CSF upon activation of transient receptor potential (TRP) vanilloid 4 (TRPV4), a calcium-permeable cation channel [47]. In the brain, Cl^- transport in the pineal gland requires ANO1 and ANO2 which is necessary for endocrine secretion of melatonin known to synchronize circadian rhythms, including sleep–wake timing [48]. In the eye, the retinal pigment epithelium (RPE) does express several anoctamins, apart from the CaCC bestrophin. Thus, native human, bovine, porcine, and mouse RPE expresses ANO1, ANO6, and ANO10. Interestingly, ANO6 and ANO10 were found in the primary cilium, while basolateral expression of ANO1 is required for Cl^- transport essential to maintain RPE retinol/retinal turnover [49]. Thus it remains unclear how much bestrophin 1 truly contributes to the basolateral Cl^- transport, and whether it might have a different function in RPE cells, such as controlling intracellular Ca^{2+} signals [50]. In this sense, and among other critical findings, Ca^{2+}-activated Cl^- currents were not found to be absent in the RPE of Bestrophin-1 knockout mice, which is discussed in [51]. Notably, our team was unable to acutely activate whole cell currents in HEK293 cells overexpressing Bestrophin 1. Apart from ANO1, 6 and 10, the Ca^{2+}-dependent PL-scramblase and non-selective cation channel ANO4, and the Cl^- channel ANO2 were detected in RPE cells, but their functions remain obscure [51–53]. Finally, ANO1 is expressed in the conjunctiva which lines the inside of the eyelids and covers the sclera, but little is known regarding ANO1's possible secretory function and contribution to aqueous humor produced in the ciliary body [53].

3. Salivary, lacrimal and other glands

In their original report on the establishment of ANO1 as a novel, bona fide, Ca^{2+}-activated Cl^- channel, Yang and colleagues demonstrated the role of ANO1 for saliva production by knocking-down expression of ANO1 using siRNA [1]. Subsequently, our lab identified ANO1 as the CaCC in submandibular acinar cells using ANO1 knockout mice [54], while the Melvin lab analyzed in great detail the role of ANO1 for saliva production in submandibular acinar gland cells [55,56]. Expression of ANO1, 2, 6, and 7 was detected in lacrimal glands and the role of TRPV4 for activation of ANO1 was demonstrated in both lacrimal and submandibular glands [53,57]. Yokoyama et al. found ANO1 in rat serous acinar and intercalated ductal cells of parotid and submandibular gland as well as mucous acinar cells of sublingual glands, while cystic fibrosis transmembrane conductance regulator (CFTR) was found in cells of excretory ducts [58]. Ca^{2+} influx provided by transient receptor potential canonical 1 (TRPC1) channels was found to be essential for activation of ANO1 in salivary gland cells [59]. It was suggested that impaired function of ANO1 leads to dry mouth disease (xerostomia), a major factor for dental caries, and may also contribute to Sjögren's syndrome [60]. Interestingly, the known circadian regulation of salivary secretion apparently correlates with the circadian expression of ANO1 in salivary glands [61]. With the help of acinar-specific ANO1-KO mice, ANO1 was found to be essential for muscarinic fluid secretion in adult mouse salivary glands [62] (Fig. 2). Apart from muscarinic ANO1-dependent Cl^- secretion, Catalan et al. reported β-adrenergic (cAMP-dependent) fluid secretion that was found to be intact in these ANO1-KO mice. Fluid secretion, however, did not require CFTR but involved a volume-regulated anion channel. Saliva pH is alkaline which is required for buffering the acidic pH in the oral cavity, and a lower salivary pH had been described in CF patients, which is due to absent CFTR function in the salivary excretory duct (reviewed in [63]). Notably, ANO1 expressed in salivary glands also conducts HCO_3^-

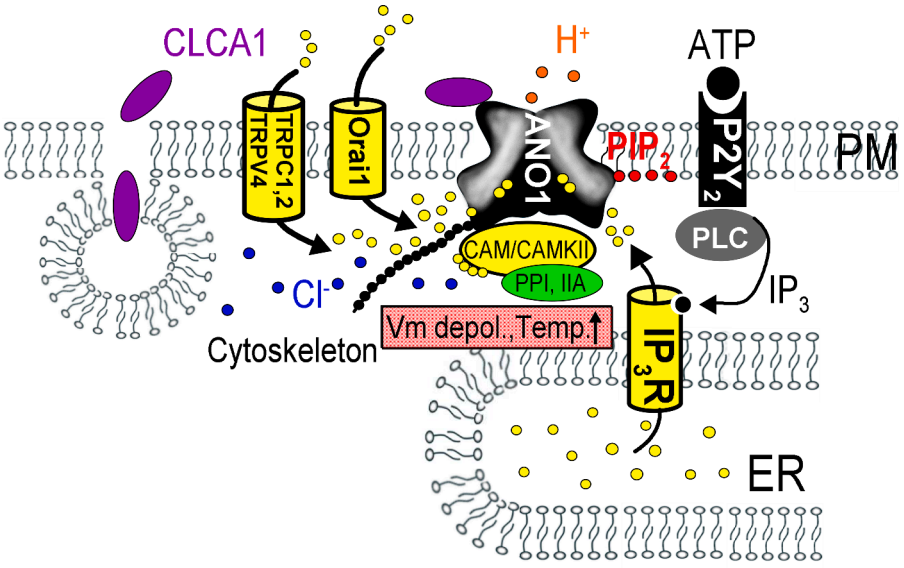

Fig. 1. *Regulation of ANO1.* Scheme summarizing regulatory properties of ANO1. Each subunit of the stable ANO1 dimer is activated by binding of two Ca^{2+} ions, which is strongly supported by depolarization of the membrane voltage (Vm). Ca^{2+} is provided primarily through receptor activated release of Ca^{2+} from the ER store, but activation through Ca^{2+} influx by Orai1 and TRP C1, C2, V4 as well as binding of calmodulin (CAM) has also been reported. Phosphorylation and dephosphorylation by calmodulin-dependent kinase (CAMKII) and protein phosphatases (PPI, IIA), respectively, may provide additional regulation. Local PM phospholipids like PIP_2 and other membrane lipids, and cytoskeletal proteins stabilize the open state of the ANO1 channel. The secreted protease CLCA1 stabilizes ANO1 expression in the PM, while extracellular protons, the intracellular Cl^- concentration and increase in temperature further affect channel activity.

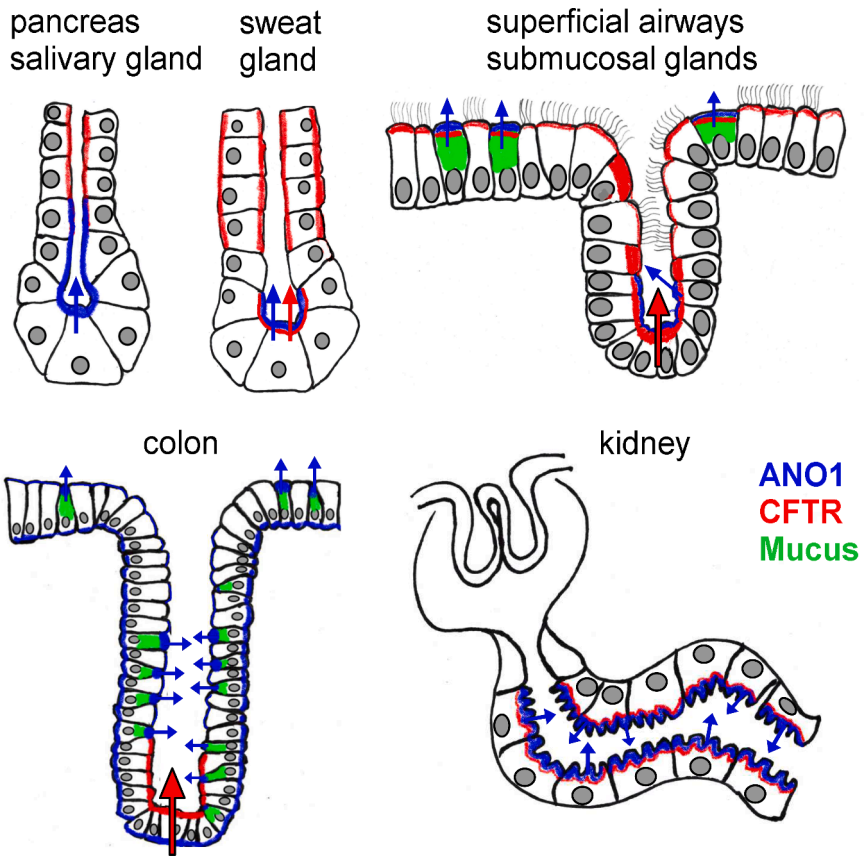

Fig. 2. *Functions of ANO1 in secretory glands, airways, intestine and kidney.* Simplified schemes indicating the Cl^- secretory function of ANO1 in different epithelial organs. Cl^- secretion by ANO1 takes place in secretory acini and intercalated cells of salivary glands and exocrine pancreas. CFTR is expressed in excretory ducts and serves as a Cl^- recycling channel necessary for HCO_3^- secretion. The sweat gland secrets Cl^- via ANO1 (clear cells) and CFTR (dark cells) and reabsorbs Cl^- in the sweat duct via apical and basolateral CFTR. Airway superficial cells express noticeable amounts of ANO1 mainly in mucus producing cells. Submucosal glands secrete Cl^- primarily via CFTR with some contribution of ANO1 (dependening on species). CFTR is found predominantly in submucosal glands and ionocytes. In the colon ANO1 is scarcely expressed in the apical membrane of columnar epithelial cells, with somewhat higher expression in goblet cells, while expression of ANO1 in the basolateral membrane of columnar epithelial cells appears more pronounced. Cl^- is secreted predominantly via CFTR expressed in the apical membrane of colonic crypt cells. In the kidney most ANO1 is expressed in the apical membrane of proximal tubular epithelial cells where it serves H^+ secretion and endocytic reabsorption of protein, and additional ANO1 expression is found in the collecting duct.

depending on the intracellular Ca^{2+} level and Ca^{2+} binding to calmodulin, which may contribute to alkalization of saliva [64]. Apart from ANO1, also ANO6 is expressed in salivary glands which, however, serves cellular volume regulation rather than electrolyte secretion [65].

In the thyroid gland ANO1 is expressed in the apical membrane of follicular epithelial cells where it is regulated by TRPC2 [66,67]. In addition to the well-established I^-/Cl^-exchanger Pendrin (SLC26A4), ANO1 could provide an apical pathway for I^- transport into the follicular lumen where it is used for iodination of thyroglobulin [68]. Apart from ANO1, pronounced expression of ANO10 was detected in the thyroid gland and in Fisher rat thyroid (FRT) cells where it regulates intracellular Ca^{2+} signals [69]. In sweat glands, ANO1 (but not bestrophin 2) is the secretory Cl^- channel necessary for cholinergic secretion of primary sweat by clear cells, while dark cells secrete Cl^- via CFTR [70]. Primary sweat is diluted due to CFTR-mediated Cl^- reabsorption and Na^+ reabsorption via ENaC during passage through the sweat duct. Interestingly, in the sweat duct CFTR is expressed in both apical and basolateral membranes [70–73] (Fig. 2). Somewhat surprising, Fujii and coworkers did not detect an inhibitory effect of ANO1 blockers on the sweat rate measured in humans in vivo, which may be due to pharmacokinetic reasons [74]. Finally, in lactating mice ANO1 was also found to be in charge of milk secretion by mammary secretory gland cells [75].

4. Lungs

ANO1 and additional anoctamins like ANO3, 6, and 9 are expressed in mouse airways and in human large and small bronchi, bronchioles and alveoli [76,77]. Using ANO1-KO mice we and others demonstrated that ANO1 is the apical CaCC in airways [54,78]. Although ANO1 clearly produced an apical Ca^{2+}-activated Cl^- current in human, mouse, and piglet airway epithelial cells, a large fraction of the transepithelial Cl^- secretion stimulated through cholinergic or purinergic agonists occurs through CFTR Cl^- channels and is supported by parallel activation of basolateral K^+ channels [79–83] (Fig. 2). ANO1 currents activated by secretagogues rapidly decline due to mechanisms described previously [15,21,34,37,84,85]. Thus, Cl^- secretion is short-lived and transient after inhibition of CFTR, comparable to the transient Cl^- secretion found in the CF airway epithelium [86–88]. Studies showed that Ca^{2+}-dependent stimulation opens ANO1 channels transiently and in parallel activates protein kinase C which is required for full activation of the dominant secretory Cl^- channel CFTR [89–91]. Moreover, muscarinic (cholinergic) stimulation augments the activity of protein kinase A (PKA) and phosphorylation of CFTR, while dephosphorylation of CFTR by tyrosine kinase is attenuated [92]. While Ca^{2+} sensitive adenylate cyclase converts intracellular Ca^{2+} signals into the second messenger cAMP, exchange protein directly activated by cAMP (EPAC1) converts cAMP into Ca^{2+} signals [93]. This partially explains why Cl^- currents activated by Ca^{2+} or cAMP in epithelial cells cannot clearly be separated

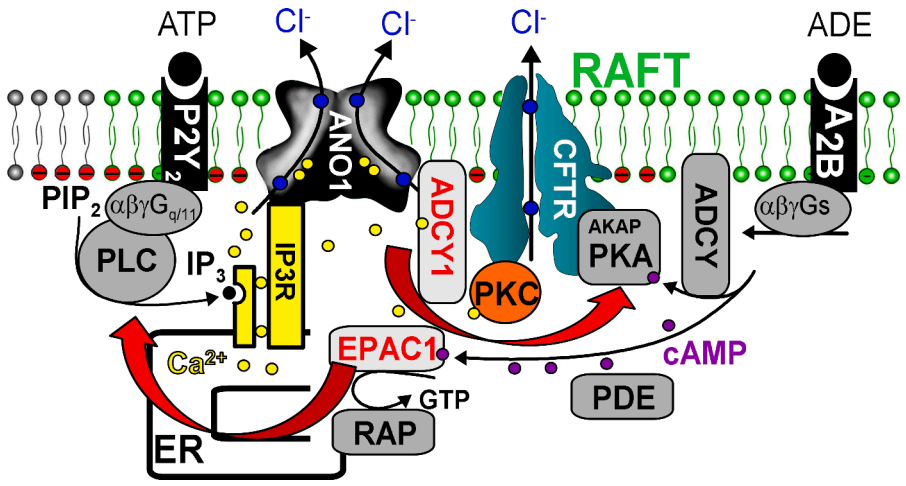

Fig. 3. *Crosstalk between Ca^{2+}- and cAMP-dependent Cl^- secretion.* Stimulation of purinergic receptors causes Ca^{2+} store release by activating IP_3 receptors. Ca^{2+} activates ANO1 and in parallel stimulates adenylate cyclase type 1 (ADCY1) to produce cAMP which activates CFTR via protein kinase A (PKA). Ca^{2+}-triggered phosphorylation by PKC fully activates CFTR. Vice versa, activation of adenylate cyclases through stimulation of adenosine receptors (A_2B) generates cAMP and activates CFTR as well as exchange protein directly activated by cAMP (EPAC1). Subsequent activation of the small GTP-binding protein RAP and phospholipase C (PLC) lead to local increase in intracellular Ca^{2+} and activation of ANO1. Receptors, ANO1, CFTR and signaling components are probably colocalized in a raft-like plasma membrane microdomain.

(Fig. 3).

Along these lines, knockout of ANO1 also affected cAMP-dependent Cl^- secretion by CFTR. As expected, knockout of ANO1 abolished Ca^{2+}-activated Cl^- secretion, but cAMP-regulated Cl^- transport was also largely attenuated in airways and colon due to loss of expression of CFTR in the apical membrane [77]. Virtually identical results were obtained in airway epithelial cells isolated from a patient homozygous for the ANO1 loss-of-function variant c.897 + 3_897 + 6delAAGT. This variant produced a largely truncated non-functional ANO1 protein [94]. Patch clamp analysis of epithelial cells isolated from this patient fully reproduced the results obtained in previous studies on ANO1-knockout mice, and showed a loss of both ANO1 and CFTR currents. The truncated ANO1 protein was expressed only in the cytosol, while expression of CFTR in the apical membrane was largely reduced [94]. Surprisingly, although both types of Cl^- currents (by ANO1 and CFTR) were basically absent, the patient did not show a CF lung phenotype, and sputum cytokine levels were only marginally enhanced in contrast to sputum from CF patients. Yet the sweat test was positive in this patient, indicating loss of CFTR function also in other tissues such as the sweat duct epithelium. We speculated whether loss of ANO1 might have prevented the development of a lung disease in this patient due to reduced mucus secretion [95].

Apart from Cl^- secretion, bicarbonate is transported by the airway epithelium. Bicarbonate is released to the apical surface in order to maintain a proper airway surface liquid (ASL) pH required for proper innate immune defense. While CFTR and the apical bicarbonate transporters Pendrin and SLC26A9 have a main role in bicarbonate secretion [96,97], ANO1 was demonstrated recently to regulate ASL pH under inflammatory conditions, i.e. after exposure to IL-4 [98]. This study may also be in support of earlier results that indicated a modulation of ANO1 bicarbonate permeability depending on Ca^{2+}/calmodulin-dependent stimulation [64].

Expression of ANO1 in the surface epithelium of healthy human and mouse airways is very low and almost undetectable by immunohistochemistry, while it shows some expression in (healthy) human airway submucosal glands. In contrast, expression of ANO1 is enhanced and is clearly detectable in submucosal glands of people with cystic fibrosis or asthma, and is also increased in airway smooth muscle [99–101]. Upon airway inflammation, e.g. in asthmatic mice, expression of ANO1 strongly increases predominantly in mucus producing cells. It was shown that expression of mucins and mucus secretion largely depends on expression and function of ANO1 [100,102-105]. Thus, ANO1 supports CFTR-dependent fluid and mucus secretion especially in airway submucosal glands [106–109]. Activation of ANO1 is currently proposed as a therapy in CF, in order to induce fluid secretion and to improve mucociliary clearance. The results from a first clinical trial with the ANO1-activator ETX001 (ETD-002) are not yet available [110,111]. Taken together, it remains to be shown whether activation of ANO1 in CF airways will be beneficial and stimulate fluid secretion in submucosal glands [112–114]. In fact, upregulation of apical ANO1 expression in asthmatic airways by tracheal instillation of the ANO1-regulator CLCA1, or topical application of the ANO1 activator Eact were shown to increase airway mucus, along with other unwanted effects [99,115,116]. The mucin MUC5AC is expressed in mucus producing cells of surface epithelium and secretory ducts of submucosal glands, and is further induced by CLCA1, probably through upregulation of ANO1 [103,115, 117-119]. CLCA1 has cytokine function and may upregulates ANO1 in both sterile and infectious inflammation [120–122].

In order to fully appreciate the role of ANO1 and other anoctamins for epithelial ion transport, it is necessary to consider their impact on Ca^{2+} signaling. ANO1 tethers the endoplasmic reticulum (ER) near plasma membrane and close to G-protein coupled receptors (GPCRs), which facilitates binding of IP_3 to its receptor thereby causing high local (compartmentalized) Ca^{2+} concentrations [123–125]. Extended synaptotagmin-1 (ESYT1) further supports ER-PM tethering and enhances PM-expression of ANO1 [126–128]. PM-Insertion of both ANO1 and CFTR requires exocytosis supported by Ca^{2+} and the phospholipid scramblase ANO6 [28,129-131]. Thus, in mice lacking expression of ANO1 or ANO6, or after siRNA knockdown of ANO1/ANO6 expression in human epithelial cell lines, expression of CFTR in the PM is largely reduced [77,132]. Moreover, knockout of ANO1/ANO6 also inhibited release of mucus in airways and intestine, and blocked secretion of lysozyme from intestinal Paneth cells [116,121,133]. Finally, release of cytokines is attenuated by inhibition or knockdown of ANO1 or ANO6 [121,122,129,134]. Based on these data we proposed inhibition of ANO1 to treat mucus obstruction in airways and gut [99,116,122, 135-137] (Fig. 4).

Apart from its role in asthma, CF and Rhinosinusitis [134,138-140], ANO1 contributes to other lung pathologies such as respiratory syncytial virus (RSV) infection, while small molecule inhibitors of ANO1 were able to inhibit infection and replication of RSV, possibly by attenuating intracellular Ca^{2+} signals [124,141,142]. Moreover, both ANO1 and

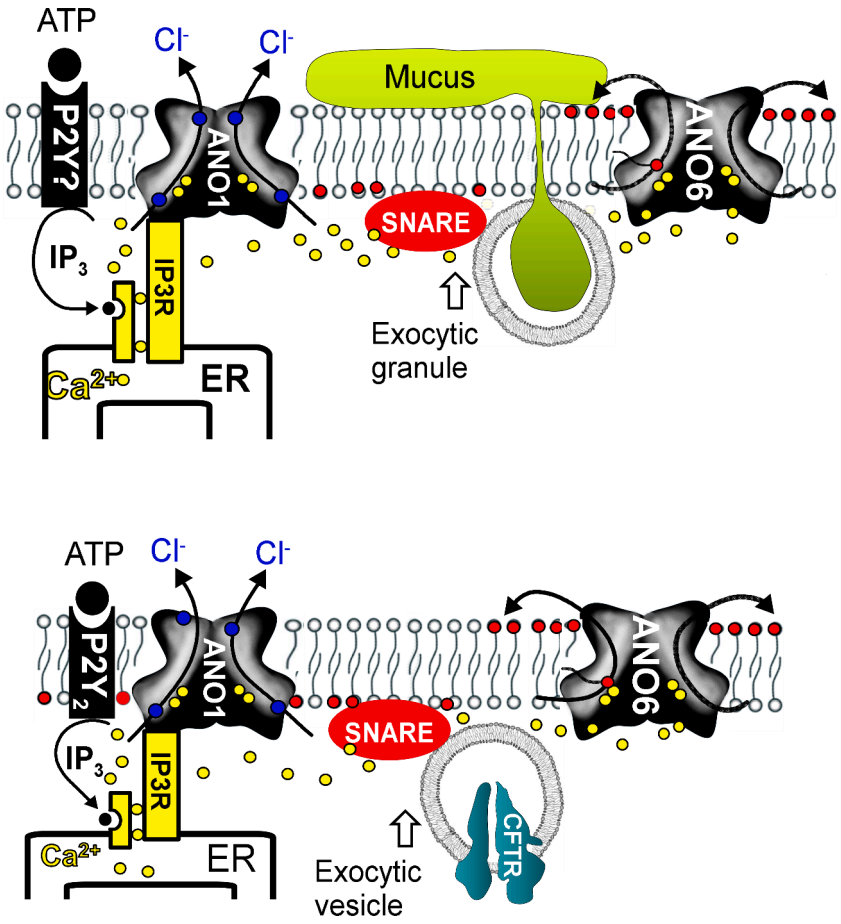

Fig. 4. *Effect of ANO1 on membrane insertion of CFTR and release of mucus.* P2Y-receptors colocalized with ANO1 lead to efficient release of store Ca^{2+} by tethering the ER. Ca^{2+} increase leads to activation of the Ca^{2+}-sensitive exocytic SNARE machinery, fusion of mucin-containing granules and release of mucus. Coactivation of ANO6 further contributes to exocytosis probably due to phospholipid scrambling (upper panel). Effective apical Ca^{2+} signaling facilitated by ANO1 causes insertion and improved expression of CFTR in the apical plasma membrane (lower panel).

ANO6 are also expressed in alveolar epithelial cells, an expression is further enhanced during inflammation [76,143]. Ca^{2+} increase and PL scrambling promote fusion of pneumocyte (alveolar syncytia) and blood coagulation induced by the spike protein of SARS-CoV-2 during COVID-19 or upon mRNA vaccination. Inhibitors of ANO1/ANO6 such as niclosamide were shown to suppress these severe complications [137, 144-147].

Finally, independent laboratories demonstrated a role of ANO1 for ciliogenesis in airways and the kidney. Reduced length of motile cilia was also observed in airways of mice which lack expression of ANO1 or ANO6, and expression of both anoctamins was observed not only in motile cilia but also in immotile renal primary cilia [42,129,148]. By mechanisms not fully understood the absence of ANO1 causes defective ciliogenesis. It could be caused by a change in the intracellular Cl^- concentration, which was proposed to act as a differentiation signal [148–150].

5. Pancreas, liver

Yang et al. identified ANO1 as the CaCC in exocrine pancreas and in several other tissues [1]. Subsequently, our team identified a defect in cholinergic Cl^- secretion in freshly isolated pancreatic acinar cells from ANO1-knockout mice [54]. Immunocytochemistry detected expression of ANO1 in the apical membrane of acinar cells, while CFTR is clearly detected in luminal membranes of intercalated ductal cells [58] (Fig. 2). HCO_3^- secretion in pancreatic ducts occurs via SLC26A6 and CFTR as a Cl^- recycling channel, which enables a high luminal HCO_3^- concentration [151]. ANO1 expressed in acinar cells provides a pathway for apical Cl^- secretion and also releases HCO_3^- into the acinar lumen to neutralize the acidic content due to exocytosis of zymogen granules [152]. In the healthy exocrine pancreas ANO1 expression is limited to the apical membrane, while much higher levels of ANO1 are diffusely expressed in pancreatic cancers [153]. Thus, ANO1 (identical to DOG1) is a common clinical marker for gastrointestinal stromal tumors (GIST) and head and neck cancers [154–156]. As outlined above, ANO1 augments intracellular Ca^{2+} signals which is strongly upregulated due to overexpression of ANO1 in pancreatic cancer [157]. It should be mentioned that another anoctamin, ANO9, was shown to promote pancreatic cancer [158]. ANO1 was also proposed as a pathogenic factor in acute pancreatitis, as it may augment IL-6 secretion through increase in intracellular Ca^{2+} and upregulation of ANO6 [124,159]. In the endocrine pancreas, ANO1 and CFTR contribute to glucose-induced oscillations of the membrane potential and support cAMP-induced insulin secretion by pancreatic ß-cells [160–162]. Finally, in cholangiocytes a role of ANO1 as secretory Cl^- channel is emerging, which may contribute to bile formation and biliary secretion. ANO1 may therefore be a susceptibility gene for gallstone formation [163–165].

6. Intestine

The intestinal epithelium does express a number of anoctamins, among them are ANO1, 6, 7, 8, 9, and 10. Expression of ANO1 is highest in distal colon but not detectable in mouse proximal small intestine [31]. There has been a long discussion about the contribution of CFTR and

CaCC to intestinal Cl^- secretion. In fact, a twin and sibling study suggested an additional CFTR-independent apical Cl^- channel in the intestine of CF patients [166]. Numerous studies, mainly performed on cultured colonic cancer epithelial cells, promoted the concept of an apical CaCC/ANO1 in intestinal epithelial cells [167]. In addition, data from patch clamping and Ussing chamber measurements as well as immunocytochemistry in small and large intestine also identified ANO1 in the apical membrane, particularly of the small intestinal epithelium [168,169], while dextran sulfate sodium-induced chronic colitis suggested a loss of apical ANO1 expression during intestinal inflammation [170]. In contrast, in a series of studies on human and murine intestine we and others identified CFTR as the only luminal exit pathway in the intestine [31,83,87,171,172] (Fig. 2). Cholinergic (Ca^{2+}-dependent) stimulation activated mainly basolateral K^+ channels via Ca^{2+} and stimulated luminal CFTR Cl^- channels via a MAP-kinase dependent pathway [173,174]. ANO1 was found to be expressed predominantly (but not exclusively) in the basolateral membrane of colonic epithelial cells [31,172,175,176]. Moreover, intestinal epithelial knockout of ANO1 inhibited Cl^- secretion activated by either Ca^{2+} or cAMP (CFTR) [77], which was confirmed in a subsequent study [168]. Measurements of $[Ca^{2+}]_i$ demonstrated that ANO1 augments Ca^{2+} signals also in the intestinal epithelium that thereby supports activation of both basolateral K^+ channels and luminal CFTR [31,77,88,168] (Fig. 2). Notably, the Verkman team found only a minor contribution of ANO1 to the apical Cl^- conductance in both intestine and airways [80,177].

ANO1 may also contribute to intestinal diseases such as diarrhea. While bacterial toxins such as cholera toxin or heat-stable enterotoxin from E. coli activate CFTR or induce inflammation and cause intestinal leakiness, activation of ANO1 was reported in the context of rotavirus-induced diarrhea [178]. Rotavirus infections leads to severe diarrhea in infants, in part due to nonstructural protein 4 (NSP4) which is an ER glycoprotein. NSP4 causes an increase in intracellular Ca^{2+} which activates both ANO1 and CFTR, and also inhibits intestinal reabsorption [179,180]. Rotavirus diarrhea is typically limited to infants and is also observed in CF infants and in mouse pups, which is possibly explained by a more apical localization of ANO1 in younger ages [180–182]. Moreover, inhibition of ANO1 was shown to suppress NSP4-induced diarrhea in mice [183,184]. Finally, ANO1 was shown to be downregulated in experimentally induced colitis in mice [170,185].

7. Kidney

ANO1 is expressed in the proximal renal tubule and to a much lesser degree in the collecting duct [186]. Using ANO1-KO mice we demonstrated that tubular H^+ secretion by the vacuolar H^+-ATPase and acidification of endolysosomal vesicles was compromised by deletion of ANO1. Acidification of endolysosomes is required for proximal tubular protein reabsorption, which is defective in ANO1-KO mice leading to proteinuria [186,187]. In ß-intercalated cells of the collecting duct ANO1 is coexpressed with CFTR and Pendrin (SLC26A4) [134]. Like in airways and intestine, ANO1 probably supports activation of CFTR which serves as a Cl^- recycling pathway for tubular HCO_3^- secretion by Pendrin [188]. Because ANO1 may support H^+ (proximal tubule) and HCO_3^- (collecting duct) secretion, this may explain why we did not observe a change in urinary pH in renal ANO1-knockout mice (unpublished).

ANO1 gained large attention as a major pathogenic factor in autosomal dominant polycystic kidney disease (ADPKD). ADPKD is a renal disease caused by mutations in the genes polycystic kidney disease 1 (85%, PKD1, polycystin 1) or 2 (15%, PKD2, polycystin 2) and often leads to terminal renal failure. In mouse and human, the renal tubular epithelium shows little proliferative activity and is predominantly reabsorptive. In contrast, in ADPKD proliferation and secretion is strongly enhanced due to upregulation of ANO1 expression [19,189-191]. Moreover, cyst growth is accompanied by renal hypoxia which activates hypoxia-inducible factor (HIF)−1α causing upregulation of purinergic receptors, a major trigger for Ca^{2+} increase, activation of ANO1 and cyst growth [192,193]. Although Cl^- secretion by CFTR was proposed in many previous studies as the major cause for cyst growth, inhibition or knockout or ANO1, but not of CFTR, inhibited cyst growth in PKD1-/- mice [191,194-198]. Upregulation of Ca^{2+} signaling due to overexpression of ANO1 is crucial for tissue hyperproliferation observed in ADPKD. It should be noted, however, that CFTR is also upregulated in ADPKD which may be of larger functional significance in humans. The authors strongly believe that the pro-proliferative effect of upregulated ANO1 is the crucial pathogenic factor in ADPKD (Fig. 5). Future experiments will tell whether ANO1 is also involved in autosomal recessive polycystic kidney disease or hepatorenal cysts [199,200]. Apart from ANO1, ANO6 is expressed in the primary cilium of renal tubular cells and supports apoptosis-dependent formation of a cyst lumen [42].

The intracellular anoctamins ANO9 and ANO10 are also well expressed in the renal tubular epithelium and are located in the ER and in the brush boarder membrane (ANO9), or in the ER right underneath the brush boarder (ANO10). The precise role of ANO9 and ANO10 in the kidney still remains obscure but it could be related to regulation of Ca^{2+} signaling (ANO9) or endo-/exocytosis (ANO10), [11,69,124]. Interestingly, the brush boarders of enterocytes and renal tubular cells can be seen as a vesicle generating organelles. By releasing extracellular vesicles, enterocytes secrete enzymes into the intestinal lumen which seem to contribute to antibacterial host defense, while urinary extracellular vesicles are analyzed for the diagnosis of inherited tubulopathies of acute kidney injury [201,202]. Massive formation of extracellular vesicles was also observed in cells overexpressing ANO1 or ANO6 [129,130,203]. Notably, both anoctamins are also expressed in growing cilia [42,129,148,149]. ANO9 and ANO10 are both scramblases and ion channels, and ANO10 has a role in endosomal sorting [46]. Organization of intracellular membrane trafficking appears to be a major task of intracellular anoctamins, probably due to regulation of intracellular Ca^{2+} signals and/or phospholipid scrambling. For ANO9 we proposed that it may lower the ER-Ca^{2+} content and augment extrusion of Ca^{2+} by the plasma membrane Ca^{2+} ATPase (PMCA), which compromises Ca^{2+}-dependent activation of ion channels and cytokine release by renal epithelial cells [11]. The ANO9 variant T604A appears to have a reduced function and was reported to be associated with chronic kidney disease [204,205]. Of note, in an earlier report, ANO9 had been identified as a cation channel that is activated by the second messenger cAMP and protein kinase A [206].

8. Reproductive tract

ANO1 is involved in numerous male and female reproductive functions, including ovarian estrogen secretion, ovulation, and sperm motility as well as acrosomal reaction, fertilization, and myometrial contraction. ANO1 was also shown to be upregulated in uterine endometrial epithelial cells in response to implantation of the embryo and decidualization [207]. Moreover, phospholipid scrambling by ANO6, activated by Ca^{2+} influx through TRPV4 is crucial for human trophoblast fusion [208].

9. Conclusion

ANO1 is present in almost all mammalian epithelial cell types, and is always coexpressed with ANO6 and additional 3–5 intracellular anoctamins. It is important to note that literally all cell types upregulate expression of ANO1 and start to proliferate after isolation from the original tissue and seeding onto tissue culture dishes [209]. Thus, ANO1 is associated with dedifferentiation, pronounced upregulation of proliferation and cancer growth [210]. Due to these circumstances, data that have been obtained exclusively from cultured cells do not provide a true image of the function of ANO1 in vivo and require therefore further validation in the original tissue. In gland acini ANO1 truly operates as a

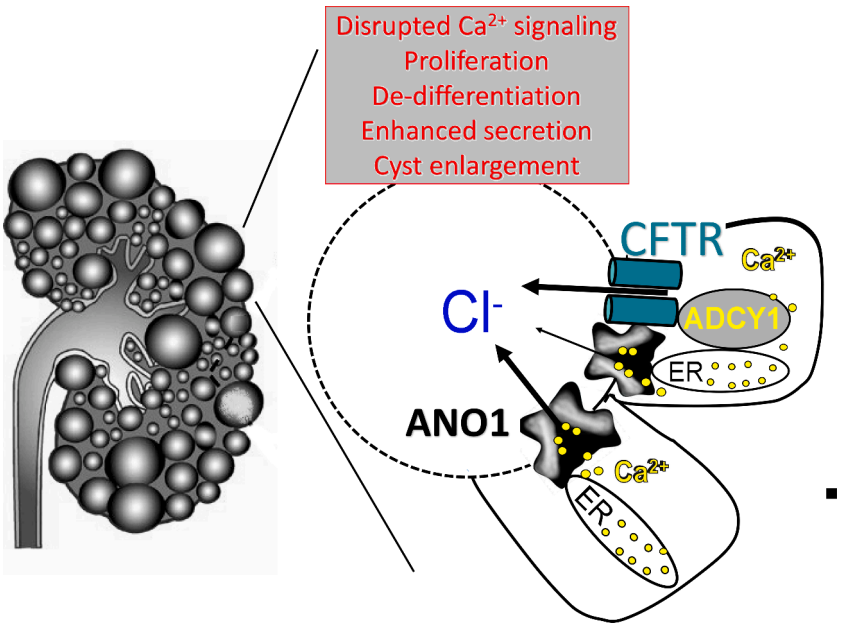

Fig. 5. *Role of ANO1 for polycystic kidney disease.* In human and mouse ADPKD expression of both ANO1 and CFTR is strongly upregulated allowing for enhanced Cl^- secretion and enlargement of developing cysts. The upregulation of ANO1 augments cytosolic Ca^{2+} signaling, which is correlated with a pronounced increase in proliferation, cellular de-differentiation and enhanced secretion, all leading to cyst formation and cyst enlargement.

secretory Cl^- channel, except of airway submucosal glands where (in humans) secretion is mainly carried out by CFTR and only to a minor fraction by ANO1. In tissues coexpressing CFTR and ANO1, ANO1 may contribute to secretion by supporting membrane expression and Ca^{2+} dependent activation of CFTR. An example is the intestinal epithelium where ANO1 supports Cl^- secretion by apical CFTR and also activates basolateral K^+ channels. Thus CFTR is in charge of both cAMP and Ca^{2+}-dependent Cl^- secretion [87]. In the healthy kidney ANO1 supports proximal tubular transport. ANO1 is upregulated in ADPKD or in renal cancer strongly enhances cell proliferation by upregulation of intracellular Ca^{2+} signaling. Anoctamins expressed in intracellular organelles may also contribute to the regulation of intracellular Ca^{2+} signals apart from controlling intracellular traffic. However, our understanding of the role of these intracellular anoctamins is only just beginning to develop.

CRediT authorship contribution statement

Rainer Schreiber: Writing – review & editing, Funding acquisition. **Jiraporn Ousingsawat:** Writing – review & editing, Methodology, Formal analysis. **Karl Kunzelmann:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Author Comments

All the authors declared no competing interests.

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