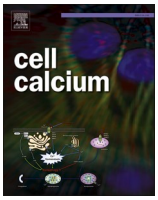
Cell Calcium 120 (2024) 102888

Contents lists available at ScienceDirect

Cell Calcium

journal homepage: www.elsevier.com/locate/ceca



Anoctamins in epithelial transport

Karl Kunzelmann *, Jiraporn Ousingsawat, Rainer Schreiber

Physiological Institute, University of Regensburg, University street 31, D-93053, Regensburg, Germany

A R T I C L E I N F O

Keywords:
TMEM16C
TMEM16D
TMEM16E
TMEM16G
TMEM16H
TMEM16J
TMEM16K
ANO3
ANO4
ANO5
ANO7
ANO8
ANO9
ANO10
Dystonia
Chronic kidney disease
Calcium signaling

A B S T R A C T

Plasma membrane localized anoctamin 1, 2 and 6 (TMEM16A, B, F) have been examined in great detail with respect to structure and function, but much less is known about the other seven intracellular members of this exciting family of proteins. This is probably due to their limited accessibility in intracellular membranous compartments, such as the endoplasmic reticulum (ER) or endosomes. However, these so-called intracellular anoctamins are also found in the plasma membrane (PM) which adds to the confusion regarding their cellular role. Probably all intracellular anoctamins except of ANO8 operate as intracellular phospholipid (PL) scramblases, allowing for Ca^{2+}-activated, passive transport of phospholipids like phosphatidylserine between both membrane leaflets. Probably all of them also conduct ions, which is probably part of their physiological function. In this brief overview, we summarize key findings on the biological functions of ANO3, 4, 5, 7, 8, 9 and 10 (TMEM16C, D, E, G, H, J, K) that are gradually coming to light. Compartmentalized regulation of intracellular Ca^{2+} signals, tethering of the ER to specific PM contact sites, and control of intracellular vesicular trafficking appear to be some of the functions of intracellular anoctamins, while loss of function and abnormal expression are the cause for various diseases.

1. Anoctamins: located in the plasma membrane and in intracellular membranous compartments

10 different anoctamins (anoctamin 1–10, ANO1-10, TMEM16A-K) constitute a family of transmembrane proteins that form ion channels and transport phospholipids (PL) between both leaflets of the plasma membrane (PM) and membranes of intracellular organelles [1]. PM-expressed anoctamins such as ANO1, 2 and 6 have been studied in great detail regarding their structure and function, while intracellularly located anoctamins are more difficult to access. A systematic analysis of the cellular localization of all ten anoctamins using suitable extracellular/intracellular immunotags or antibodies is still pending, so that there are uncertainties regarding their actual cellular localization, especially in native cells. We and others have analyzed the cellular expression of overexpressed GFP-tagged anoctamins as well as endogenous anoctamines with a number of different antibodies, yielding different results depending on the detection method and cell type or tissue examined [2–5]. So far there is agreement that the Cl^- channels ANO1 and ANO2 as well as the PL scramblase ANO6 are clearly located in the PM [1]. According to current data, the short isoform of ANO7, as well as ANO8 and ANO10 appear to be expressed only in intracellular compartments, while ANO3,4,5,7 (long isoform) and 9 can be detected in the PM. When expressed in Fisher rat thyroid (FRT) these anoctamins are found more frequently in the PM, which might be related to the unusual membrane sorting observed in these cells [4,6]. Ca^{2+} activation of these so-called intracellular anoctamins is currently not well defined, but since the last comprehensive review on anoctamins by Pedemonte and Galietta, new data on intracellular anoctamins are now available, slowly revealing their biological function and clinical significance [1].

2. Anoctamins, TMC and OSCA/TMEM63 channels form proteolipidic pores

The molecular structure of the scramblases ANO6 and ANO10 and mechanisms of lipid scrambling have been reported [7–9]. These anoctamins form peculiar transmembrane pores which are partially shaped by membrane phospholipids. In particular, anoctamin scramblases, the transmembrane channel-like (TMC) proteins and the large

* Corresponding author.
E-mail address: karl.kunzelmann@ur.de (K. Kunzelmann).

https://doi.org/10.1016/j.ceca.2024.102888
Received 20 February 2024; Received in revised form 15 April 2024; Accepted 16 April 2024
Available online 17 April 2024

family of hyperosmolality-operated calcium permeable channels (OSCA) all share such proteo-lipid pores as a common structural feature [10]. TMC proteins are required for mechanosensory transduction in inner ear hair cells, regulate intracellular Ca^{2+} signals and cell volume, and have a pathogenic role in human papillomavirus infection [11,12]. Although not yet shown they may also scramble membrane phospholipids [13]. OSCA/TMEM63 channels are the largest family of mechanosensitive channels in plant and mammalian mechanotransduction [10], which are also detected in lysosomes [14]. Regulation by mechanical stress has been also reported for anoctamins in lens cells and biliary epithelium [15,16], while we found cell volume (cell swelling) dependent regulation of ANO1,6,10 and other anoctamins [17–19]. It will therefore be interesting to further investigate the importance of mechanosensitive regulation for the function of intracellular anoctamins. For completion it should be noted here that also G-protein-coupled receptors (GPCRs) are able to scramble phospholipids, which may be relevant to some of the observations described in this review [20].

3. ANO3, an intracellular scramblase and ion channel expressed in the brain

ANO3 (TMEM16C) is expressed predominantly in cerebral cortex, cerebellum, hippocampus, and caudate [4]. It also shows some expression in glands, lung and male reproductive tract (https://www.proteinatlas.org). ANO3 has been shown to operate as a PL scramblase [21,22]. We detected ANO3 scramblase activity when overexpressed in HEK293 cells and, in addition, demonstrated an ANO3 whole cell current that can be activated by the Ca^{2+} ionophore ionomycin [23]. Thus ANO3 is a PL scramblase which also conducts ions, similar to other anoctamins like ANO5, ANO6, and ANO10 [3,4,9,24–26]. Importantly, scramblase activity of ANO3 was detected in cells in which expression of the ubiquitous endogenous scramblase ANO6 [27], had been knocked out [4]. ANO6 is expressed in every cell type and thus unintended Ca^{2+}-dependent activation of endogenous ANO6 during overexpression of other anoctamins may lead to misinterpretations [5]. In patch clamp experiments Suzuki et al. did not detect an additional whole cell current in ANO3-overexpressing cells using a cytosolic (pipette) Ca^{2+} concentration ($[Ca^{2+}]_i$) of 500 nM. This, however, is not surprising as activation of anoctamin scramblases/ion channels requires $[Ca^{2+}]_i$ of 1 μM or higher [24,28,29]. Although ANO3 can reach the PM when overexpressed, endogenous protein is probably located in intracellular compartments [9,19,23,24,30,31].

4. ANO3 in dystonia

Numerous ANO3 variants were found in patients with dystonia, a neurological disorder that is characterized by abnormal movements and postures caused by involuntary muscle contractions [32]. Dysfunctional neuronal K^+ channels can cause instability of the membrane resting potential that will lead to neuronal hyperexcitability and involuntary muscle activity. In fact, Ca^{2+}-activated K^+ channels like the large conductance KCNMA1 channel and particularly members of the small/intermediate conductance KCNN family are expressed in basal ganglia and especially in neostriatal neurons. Mutations within these genes are known to cause dystonia, while Ca^{2+}-activated KCNN K^+ channels are key modulators of neuronal activity in the striatum [33–38]. These channels are activated through purinergic stimulation, which leads to an increase in intracellular Ca^{2+} ($[Ca^{2+}]i$), binding of Ca^{2+}/calmodulin (and possibly Ca^{2+}/hippocalcin) to KCNN2 K^+ channels, causing hyperpolarization of neurons [39–41] (Fig. 1).

We recently compared Ca^{2+} signaling and activation of ion channels in cells expressing wild type ANO3 with cells expressing ANO3 variants causing dystonia. We showed that ANO3 operates as a Ca^{2+}-activated phospholipid scramblase and conducts ions as well [23]. Fibroblasts obtained from dystonia patients who carry ANO3 variants showed abnormal Ca^{2+} signaling and impaired activation of K^+ channels. The data also suggest that ANO3 is expressed in the endoplasmic reticulum (ER), possibly regulating ER Ca^{2+} store content and activation of K^+ channels. The data suggest an increased Ca^{2+} sensitivity for some ANO3 variants causing enhanced basal cytosolic Ca^{2+} levels and inhibition of receptor-mediated ER Ca^{2+} store release [42,43]. Thus, activation of KCNN channels is attenuated causing impaired neuronal repolarization and hyperexcitability. In addition, enhanced PL scrambling by ANO3 variants may affect the viability of striatal cells in vivo. However, enhanced basal PL scrambling could also lead to mistargeting of the ER to irregular ER/PM membrane contact sides (MCSs), thereby unbalancing intracellular Ca^{2+} homeostasis (Fig. 1). Corresponding to this hypothetical role of ANO3, the paralogous scramblase ANO10 was recently shown to regulate endosomal sorting, which is discussed below [30].

KCNN channels are activated by Ca^{2+}/calmodulin and participate in slow afterhyperpolarization triggered by ER Ca^{2+} release channels and voltage gated Ca^{2+} channels at ER-PM junctions, with a contribution of hippocalcin as Ca^{2+} binding protein [44]. Mutations in the neuron-specific hippocalcin also cause dystonia [45,46]. Hippocalcin is mainly expressed in striatal neurons and undergoes a conformational change upon binding of cytosolic Ca^{2+}, leading to its translocation from the cytosol to the plasma membrane (reviewed in [47]). Translocation of

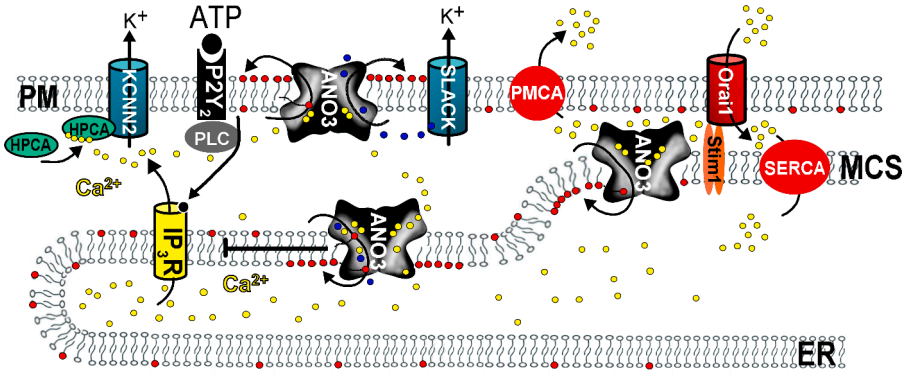


Fig. 1. Hypothetical role of ion channel function and phospholipid scrambling by ANO3 for Ca^{2+} signaling and activation of K^+ channels and malfunction in dystonia. ANO3 is an ER-localized PL scramblase and probably a nonselective ion channel with potential expression also in the PM of neurons. PL scrambling by ANO3 could take place in the ER and inhibit release of Ca^{2+} and thus activation of KCNN K^+ channels through the Ca^{2+} binding calmodulin-homologue hippocalcin (HPCA). PL-scrambling could also contribute to formation of PM/ER membrane contact sides (MCS) thereby affecting intracellular Ca^{2+} signaling. Augmented PL scrambling by ANO3 variants may lead to enhanced cell death of striatal neurons. ANO3 has also been reported to interact with Na^+ activated K^+ channels (SLACK). PM-localized ANO3 may allow influx of Na^+ supporting stimulation of Na^+-activated SLACK.

hippocalcin is required for activation of K^+ currents which limits neuronal spike frequency by slow afterhyperpolarization. Dystonia causing variants of hippocalcin prevent translocation of hippocalcin and thus activation of K^+ currents, causing depolarization of the membrane voltage, enhanced Ca^{2+} influx and inappropriate release of synaptic vesicle [47] (Fig. 1).

5. ANO3 – a partner of neuronal K^+ channels controlling excitability

ANO3 was also reported as binding partner of Na^+ activated K^+ channels (K_{Na}, SLACK), which are known to dampen neuronal excitability [48]. ANO3 obviously interacts with Slack, thereby enhancing sodium sensitivity and increasing single-channel activity at low intracellular sodium concentrations, thereby enabling K_{Na} currents under physiological conditions. ANO3 knockout rats show a significant reduction of K_{Na} currents causing a decreased threshold for action potential firing and enhanced neuronal activity. Eliminating expression of ANO3 in rats increased thermal and mechanical sensitivity with hyperalgesia [48,49]. Thus, ANO3 contributes thermoregulation and protection against febrile seizures in rat pups and humans [50–52]. Further reports suggest a role of ANO3 for other cerebral diseases such as cluster headache or Huntington disease [53,54], inflammatory diseases like osteoarthritis and eczema [55,56]. All of these findings demand further investigations to address many open questions like: How exactly does ANO3 regulate Slack activity and is $[Ca^{2+}]_i$ involved? Is ANO3 expressed in the plasma membrane of neurons and what is the contribution of PL scrambling by ANO3?

6. ANO4: another intracellular scramblase and ion channel affecting $[Ca^{2+}]_i$

Earlier patch clamp studies from our laboratory showed that overexpression of ANO4 (TMEM16D) in HEK293 cells induced a Ca^{2+}-activated whole cell currents with linear current/voltage relationship [3]. These nonselective currents were activated by ionomycin or by stimulation of GPCRs followed by release of Ca^{2+} from the ER store [3]. GFP-tagged ANO4 appeared to be localized in or close to the PM. Subsequent studies indicated ER-expression of ANO4 causing Ca^{2+}-release and activation of endogenous ANO6 currents [5]. Duran et al. also detected intracellular expression of ANO4 but found no ion currents related to ANO4 overexpression [31]. However, in their paper they also did not detect currents related to overexpression of ANO6, while meanwhile ANO6 is clearly identified as PM-expressed Ca^{2+}-activated PL scramblase with ion channel properties [3,4,7,27–29,57–60]. Finally, Reichhart et al. reported ANO4 as a Ca^{2+}-activated cation channel and provided some evidence for expression of ANO4 near the basolateral membrane of the retinal pigment epithelium [61].

PL scrambling by ANO4 was first demonstrated by Suzuki and coworkers, while Gyobu et al. identified a so-called scrambling domain (SD) in ANO6, which is also present in ANO4 and all other intracellular anoctamins [21,62]. SDs are essential for PL transport, and were found in all other anoctamins except of ANO1 and ANO2, and does not seem to be functional in ANO8 (c.f. below). We localized ANO4 in the ER and found that it interacts with the ER Ca^{2+} pump SERCA [5]. Taken together ANO4 is most likely an ER-localized Ca^{2+} regulated PL scramblase that may also be expressed in the PM of native, i.e. differentiated cells. ANO4 is likely to control der PL content in the cytoplasmic leaflet of the ER-membrane, similar to ER-scramblase ANO10 [63]. PL scrambling by ANO4 (and other ER-localized scramblases) may lower the abundance of negatively charged PtdSer or other types of negatively charged PLs in the outer ER membrane leaflet, thereby generating a signal for translocation and generation of MCSs. This is discussed in more detail below for ANO10 [63].

IP_3-triggered Ca^{2+} release from the ER was strongly attenuated in cells expressing ANO4, presumably due to a reduced ER Ca^{2+} store content or activation of PKC by enhanced basal $[Ca^{2+}]i$ (which is known to inhibit IP_3R) [5]. Ca^{2+} permeability of ANO4 might cause an ER Ca^{2+} leak, or support Ca^{2+} leakage by operating as a counter-ion channel [64]. Accordingly, lower ER Ca^{2+} levels in ANO4 expressing cells could be the reason for attenuated IP_3 - dependent activation of KCNN4/SK4 K^+ channels or ANO1 Cl^- channels, similar to the effects described for ANO3 on activation of KCNN2 [5]. Interestingly, a similar inhibition of GPCR/IP_3/Ca^{2+}-dependent activation of ANO1 was also observed for the anoctamin homologue TMC8 [12,65]. As described above, TMC proteins also form proteo-lipidic pores and could potentially scramble membrane phospholipids [13]. Activation of ANO6 by a putative ANO4-induced ER Ca^{2+} leak, was also shown to activate constitutive Ca^{2+}-dependent PL scrambling leading to membrane shedding [66]. Although many details are still missing, we speculate that ANO4 redirects Ca^{2+} signals to PM compartments containing ANO6 and Ca^{2+} influx channels. In support of this, a functional interaction of ANO6 with Orai1 has been found [5,18]. In contrast, ANO1 and the yeast ANO1-homologue Ist2 target the ER and IP_3 receptors (IP_3R) near GPCRs [65].

7. ANO4 in organ physiology and pathology

ANO4 was described as a negative regulator of aldosterone secretion in the zona glomerulosa of adrenal glands [67]. Overexpression of ANO4 attenuated calcium-mediated aldosterone secretion and cell proliferation. ANO4 was found to be expressed in intracellular compartments. It was speculated that the inhibitory effects of ANO4 on intracellular Ca^{2+} signals may be responsible for inhibition of aldosterone secretion in the presence of ANO4. Apart from endocrine tissues, ANO4 is predominantly expressed in the brain. Brain glucose-sensing neurons in the hypothalamus are essential to keep blood glucose levels at stable levels in order to prevent severe hypoglycemia. ANO4-expressing glucose-inhibited (ANO4-plus) neurons in the ventromedial hypothalamic nucleus increased their firing activity under low-glucose conditions, thus causing food intake [68]. In contrast, ANO4-minus neurons of the same hypothalamic region that do not express ANO4 are inhibited by high glucose, thereby suppressing food intake. Moreover, enhanced appetite and rise of blood glucose levels by stimulation of ANO4-plus neurons in mice was suppressed by knockout of ANO4 [68,69]. Notably, large-scale human exome sequencing further detected an ANO4 variant that is associated with human obesity [70]. It was proposed that in ANO4-minus neurons, K_{ATP} channels are activated by hypoglycemia and hyperpolarize neurons, while in ANO4-plus neurons K_{ATP} currents are largely absent. This may be due to a lower ER Ca^{2+} load due to ANO4-induced Ca^{2+} leak, or due to differential MCSs in ANO4-expressing cells [70]. The subcellular localization of ANO4 in hypothalamic neurons is currently unclear, and the effects of ANO4 on intracellular Ca^{2+} signals have not yet been assessed in these neurons. Considering that ANO4 expression almost abolished receptor-mediated activation of SK4 K^+ channels in our studies, we speculate a similar scenario for hypothalamic ANO4-plus neurons [5]. ANO4 is found in most regions in the brain (https://www.proteinatlas.org/ENSG00000151572-ANO4/brain) and therefore the discovery of many more ANO4-related brain diseases can be expected for the future [71,72]. The overlapping properties of ANO3 and ANO4 suggest that these close paralogues may operate in similar ways (Fig. 1).

8. ANO5 - a phospholipid scramblase and ion channel required for plasma membrane repair and thrombus formation

ANO5 is highly expressed in the GI tract and the skeletal muscle [4] (https://www.proteinatlas.org/ENSG00000185101-ANO5/tissue). The role of ANO5 in muscle disease and gnathodiaphyseal dysplasia has been reviewed recently [73,74]. We will therefore focus only on novel functional and cell biological aspects of ANO5. The PL scramblase activity of ANO5 was demonstrated initially by Suzuki et al. [21] and was later

confirmed by Gyobu and coworkers [62]. The latter study is probably more significant as PM-expression of the scrambling domain was better controlled [21]. In this paper the authors detected no channel activity for ANO5 (and neither for ANO4, 6, 8, 9, 10). However, as all patch clamp experiments were done in the presence of (only) 500 nM pipette Ca^{2+}, $[Ca^{2+}]_i$ was probably too low to activate these anoctamins [21]. Subsequent studies clearly demonstrated that ANO5 also operates as nonselective ion channel, which could be relevant for the fusion of muscle precursor cells [24,75].

9. ANO5 in muscle disease and muscle cell repair

Cells are exposed to mechanical stress in many types of tissues, potentially causing an injury of the plasma membrane. Skeletal muscle cells are probably among the tissues which experience the most extensive mechanical stress. This is particularly evident in sore muscles after extensive exercise, caused by disruption of muscle fibers [76]. Thus, repair mechanisms need to be in place to reseal broken plasma membranes. Mutations in the ANO5 gene participate in different types of skeletal muscle diseases including autosomal recessive limb-girdle muscular dystrophy, where a defect in muscle cell repair has been suggested [73,74,77]. Chandra et al. proposed a role of ANO5 as an ER-localized Cl^- counterion channel that is required to balance SERCA mediated uptake of Ca^{2+}, which has entered the cell during cell damage. Apart from Cl^- transport ANO5 also shows some permeability for cations and demonstrates a liner current/voltage relationship in the presence of asymmetric Cl^- concentrations [3,24,26,78]. In addition to mitochondrial depolarization and $[Ca^{2+}]_i$ increase [78], a pronounced depolarization of the membrane voltage and an additional increase in intracellular Cl^- and Na^+ concentrations would be expected during rupture of skeletal muscle PM, which, however, has not yet been examined in detail. According to Chandra et al., SERCA-mediated ER-uptake of Ca^{2+} is essential to avoid any interference of excessive $[Ca^{2+}]i$ with the healing process, while ER Ca^{2+} uptake is compromised in the absence of ANO5 [79]. Charge compensation by counterion mechanisms during ER-store release and SERCA-mediated ER-refill has been reported in smooth, skeletal and heart muscles as well as epithelial cells [64,80–84]. Lack of efficient counterion transport can lead to extension of the ER-lumen and Ca^{2+} precipitations.

Moreover, ANO5 may be able to balance charge movement also by operating as a nonselective cation channel instead of transporting Cl^- ions into the ER as proposed by Chandra et al. [24]. However, a very different function of ANO5 was described by Foltz et al., who presented data that show a role of ANO5 located within the PM. By accumulating around the membrane defect, ANO5 serves as an anchor for annexins required for repair of sarcolemmata. Although PL scrambling is induced around the defect, the scramblase function of ANO5 appears not to be required for the repair. However, PM expression might be higher for the scrambling-deficient ANO5/ANO1 chimera that has been used in this study, thus masking the true contribution of ANO5 scrambling to membrane healing [85]. As shown for other anoctamins, expression of ANO5 in ER or PM might depend on the level of activation (c.f. above). PL scrambling observed during repair of sarcolemmata does most likely also occur through ANO6, and thus the healing process may not strictly require ANO5 scramblase activity (https://www.proteinatlas.org/ENSG00000185101-ANO6/tissue) [4]. These and other ambiguities about PM repair in skeletal muscle still need to be clarified (Fig. 2A).

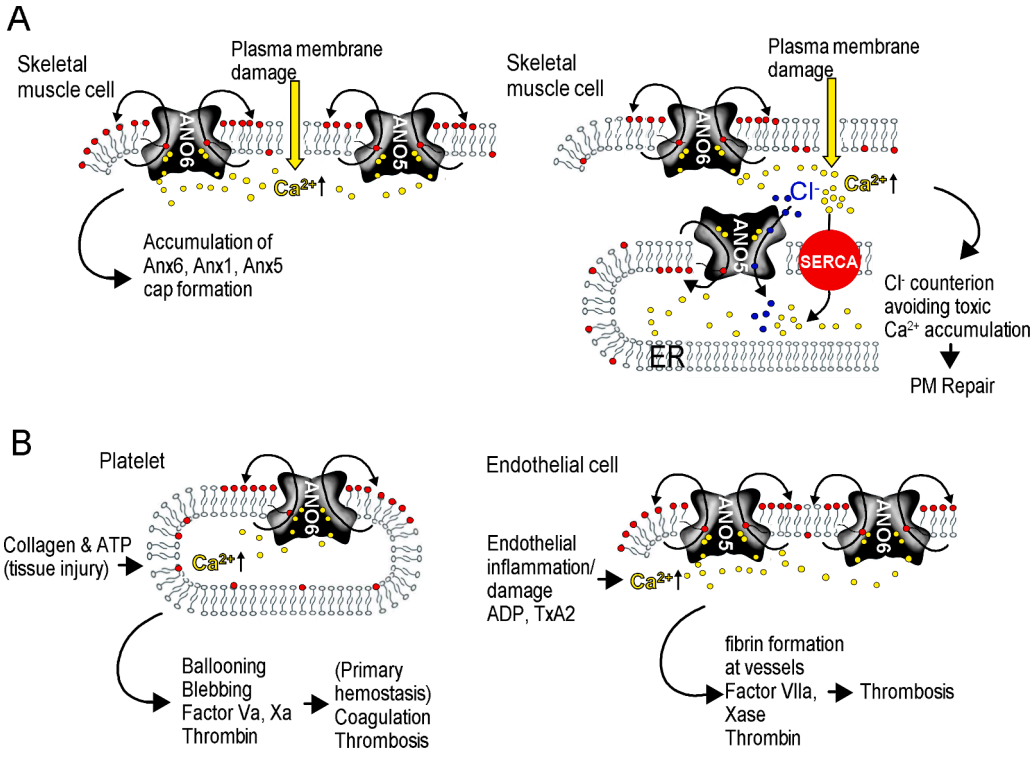


Fig. 2. Proposed mechanisms for ANO5 mediated skeletal muscle repair and endothelial triggered thrombosis. A) Two different concepts were proposed for ANO5 mediated repair of skeletal muscle PM. Rupture of the PM allows passive entry of Ca^{2+} which will trigger accumulation of annexin (Anx) 6, 1, and 5 forming a repair cap, facilitated by ANO5 anchorage. Scrambling by ANO5 (and ANO6) is induced, but scrambling by ANO5 is not essential for repair (left). Another concept predicts localization of ANO5 in the ER, where it serves as a Cl^- permeable channel required to balance massive uptake of positive charges into the ER by SERCA. This avoids toxic cytosolic Ca^{2+} levels which would otherwise interfere with PM repair (right). B) Blood coagulation and thrombosis by platelets and endothelial cells. Platelets express large amounts of ANO6 (but no ANO5) and are activated during primary haemostasis and blood coagulation, which may lead to thrombosis (left). Endothelial cells express ANO5 and ANO6 which are both activated during inflammation and/or endothelial damage with release of ADP and thromboxane (Tx) A2. Inhibition of endothelial PL scrambling interferes with endothelial thrombosis but still allows coagulation by platelets (right).

10. Gnathodiaphyseal dysplasia, thrombosis and fertility

As described above, gain of function of in ANO5 can cause enhanced scrambling activity leading to gnathodiaphyseal dysplasia, a skeletal disorder causing jaw deformities and long bone fractures [75]. Oscillations of $[Ca^{2+}]_i$ is essential for differentiation of bone cells. Receptor activator of NF-κB ligand (RANKL) is a member of the tumor necrosis factor (TNF) cytokine family, which induces oscillatory changes in $[Ca^{2+}]_i$, resulting in Ca^{2+}/calcineurin-dependent dephosphorylation and activation of nuclear factor of activated T cells c1 (NFATc1). NFATc1 then translocates to the nucleus and induces bone cell-specific gene transcription to allow differentiation of osteoclasts [86]. In mice, ablation of Ano5 reduced $[Ca^{2+}]_i$ transients in bone cells, which induced defective osteogenesis and osteoclastogenesis, therefore resulting in bone dysplasia [87]. Moreover, decrease in ANO5 expression impaired RANKL-induced oscillations of $[Ca^{2+}]_i$ in osteoclasts. ANO5 deletion in mice diminished $[Ca^{2+}]_i$ oscillations in both osteoblasts and osteoclasts, causing reduced WNT/β-Catenin and RANKL-NFATc1 signaling. RANKL-induced $[Ca^{2+}]_i$ oscillations require repetitive ER Ca^{2+} release by IP_3 receptor channels with activation of store-operated Ca^{2+} entry [86]. Thus the paper by Li et al. strengthens the role of ANO5 as a positive regulator of intracellular Ca^{2+} signaling. Interestingly, a close paralogue of ANO5, the PM scramblase ANO6, also augments receptor mediated store release by a mechanism that currently remains obscure [5]. It is well established that ANO6-mediated PL-scrambling in platelets (thrombocytes) is critical for hemostasis and thrombosis [88].

In addition to ANO6, ANO5 was shown to regulate endothelial procoagulant activity and thrombus formation, a finding that could be of major clinical significance in the future [89]. Obviously both ANO5 and ANO6 support coagulation and thrombus formation initiated at the surface of endothelial cells. In their thrombosis model Schmaier et al. showed that endothelial PtdSer exposure is even more pronounced than in platelets. Excitingly, the anoctamin inhibitor benzbromarone prevented PtdSer externalization and procoagulant activity by endothelial cells, and protected mice from thrombosis without increase in bleeding, i.e. primary haemostasis and coagulation seemed to be still functioning. This is explained by the fact that platelets lacking expression of ANO5 are still partially functional. As thrombosis occurs preferably at the endothelial cell surface, these results could form the basis of a novel anticoagulant therapy, based on specific inhibitors for ANO5 [89] (Fig. 2B). Apart from physiological pathogenic functions, ANO5 appears to have a role in reproduction. Gyobu et al. found ANO5 expressed in the tail of mouse sperms. Knockout of ANO5 caused decreased fertility which was caused by reduced sperms motility [90]. It will be interesting to learn whether variants of ANO5 can be a possible cause for infertility in humans.

11. ANO7 and ANO8

Molecular insights into the cellular functions of ANO7 are limited. ANO7 is best known for its association with various types of cancer, in particular prostate cancer [91]. It is weakly expressed in a number of tissues including cartilage, spleen, prostate, and predominantly in the GI tract. We and others found that overexpressed ANO7 is mostly intracellular and only weakly detectable in the plasma membrane. A small ionomycin-activated whole cell conductance was found to be associated with overexpression of ANO7 [3,4,31,92]. PL scrambling by the ANO7 scrambling domain was shown by Gyobu et al. [62]. Another study suggested an interaction with intracellular vesicular proteins, which is interesting in the context of recent reports on ANO10 showing a role of this anoctamin as intraorganellar regulator of endosomal sorting [30,63,93]. In prostate epithelial cells ANO7 has been reported as PM-located anoctamin preferentially found at apical/lateral cell-cell contact sides. However, during dedifferentiation and formation of prostate cancers this pattern was changed towards a more diffuse expression of ANO7 [92].

ANO8 is expressed at low levels in most tissues. It is a large protein containing 1232 amino acids and thus an atypical member of the anoctamin family, with an extended C-terminal sequence [3,4]. Upon overexpression it did not cause a significant whole cell current, even when targeted to the PM, but in contrast reduced basal whole cell. Moreover, the ANO8-SD has lost its ability to scramble PL [4,62]. However, the large size of ANO8 provides the molecular length necessary to bridge the distance between ER and PM. In fact, Jha et al. demonstrated ANO8 as a tether that establishes MCSs between the ER and phosphatidylinositol 4,5-bisphosphate (PIP_2)-rich PM domains [94].

PIP_2 comprises only about 1 % of the phospholipids in the cytoplasmic leaflet of the PM, yet it regulates many distinct cellular processes through spatial organization [95,96]. MCSs, i.e. ER/PM junctions are the sites where the ER contacts the PM by protein/protein interactions and/or through ER- or PM-localized tether proteins. Due to its role as a tether, ANO8 allows effective STIM1-STIM1 and STIM1-Orai1 interactions and activation of Orai1 in phosphatidylinositol 4,5-bisphosphate (PIP_2) rich PM compartments. Within these signaling compartments all core Ca^{2+} signaling proteins are assembled, like Orai1 (calcium release-activated calcium channel protein 1), PMCA (Plasma Membrane Calcium ATPase), STIM1 (Stromal Interaction Molecule 1), IP_3R (Inositol 1,4,5-trisphosphate Receptor), and SERCA (Sarco/Endoplasmic Reticulum Calcium ATPase) [94]. Importantly, $[Ca^{2+}]_i$ enhanced by ER-release or SOCE (Store-Operated Calcium Entry) is pumped back again into the ER by SERCA, or pumped out of the cell by PMCA to generate Ca^{2+} oscillations and to avoid toxic effects due to sustained high $[Ca^{2+}]_i$ levels. Moreover, Orai1/Stim1 channels are inhibited through interaction with SARAF (Store-operated Calcium Entry-associated Regulatory Factor) (SARAF) and calmodulin. Stim1 is well known for its role in SOCE, but it also directly interacts with PMCA to inhibit PMCA-mediated Ca^{2+} extrusion, which is of particular importance in *T*-cell signaling [97]. ANO8 was reported to facilitate Orai1 channel activation and to slow SARAF-independent Orai1 inactivation [94]. Corresponding to these findings we found that GPCR/IP_3-triggered Ca^{2+} release from the ER was attenuated by overexpression of ANO8, while store emptying by inhibition of SERCA and SOCE was augmented [5]. ANO8 might translocate the ER away from MCS containing GPCR/ANO1/IP_3R (ER Ca^{2+} efflux side) and shift it towards MCS containing Orai1/Stim1/PMCA/SERCA (i.e. the ER Ca^{2+} influx side), which would be a mechanism we proposed recently for ER-expressed ANO9 and ANO4 [98]. Apart from ANO8 three different extended synaptotagmins (E-Syt1-3) we shown to participate in formation of ER/PM junctions [99]. E-Syt1 is known to tether ER/PM in a PIP_2 and Ca^{2+} dependent manner [99,100]. Interestingly, E-Syt-dependent MCSs are not required for SOCE and SERCA-mediated refill of the ER Ca^{2+} store [99]. Yet, Ca^{2+} influx was shown to be required for extended E-Syt1-induced ER-plasma membrane tethering [101] (Fig. 3).

The PM-located Ca^{2+}-activated Cl^- channel ANO1, a homologue of yeast Ist2, can also be regarded as a membrane tether given its direct interaction with the IP_3R [5,102]. In a microscopic PM traffic assay for ANO1, we identified the three extended synaptotagmins (ESYT1–3) as ANO1 traffic enhancers. Knockdown, particularly of E-Syt1, attenuated expression of ANO1 in the PM and inhibited activation of ANO1 currents [103]. For the yeast ANO1 homologue Ist2, it was shown that it recruits the ER to the PM and it may even slip directly from the peripheral (cortical) ER into the plasma membranes in a Golgi-independent manner (unconventional protein secretion; UPS) [104]. Interestingly, the ER to Golgi transport inhibitor brefeldin A abolished glycosylation of ANO1 but did not affect PM expression and activation of ANO1, indicating UPS also for ANO1 [105]. The mechanisms of unconventional (non-canonical) protein secretion are poorly understood, but UPS could explain why anoctamins are frequently detected in both ER and PM [106].

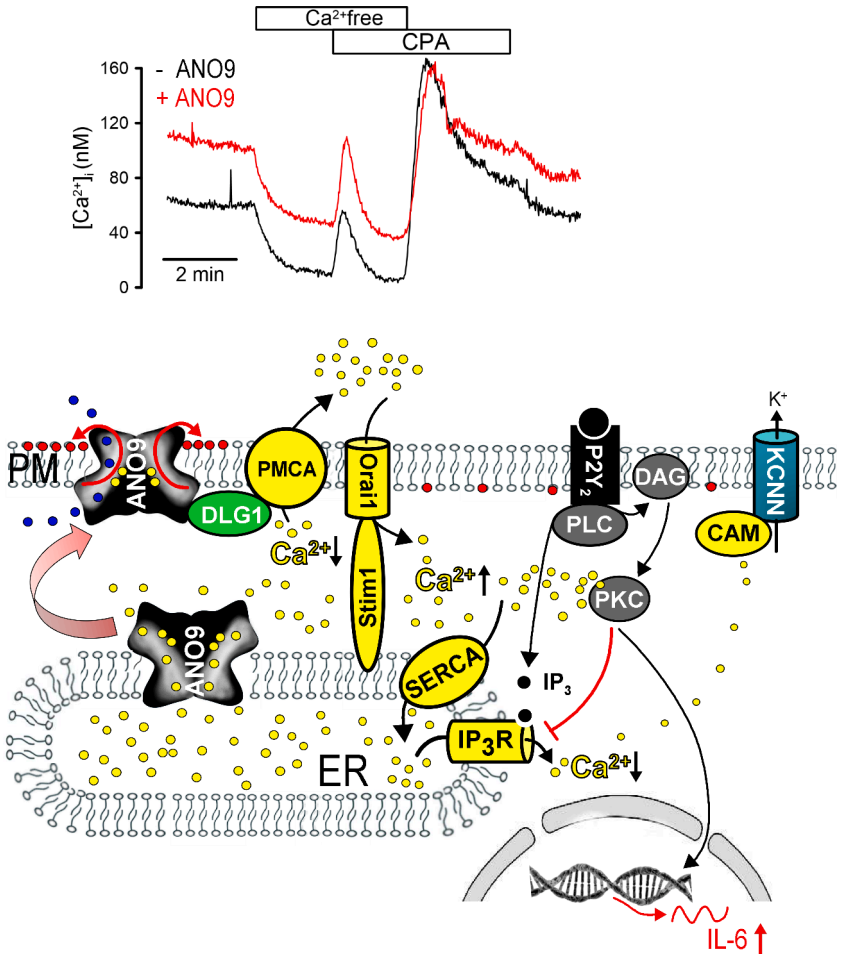


Fig. 3. Proposed role of ANO9 for Ca^{2+} signaling and chronic kidney disease. Upper panel: Intracellular Ca^{2+} measured by Fura2 in HEK293 cells in the absence or presence of ANO9. Expression of ANO9 in cell lines caused enhanced basal Ca^{2+} levels possibly by producing an additional ER Ca^{2+} leak. ANO9 had no effect on store emptying by inhibition of SERCA with cyclopiazonic acid (CPA) or peak Ca^{2+} levels induced by SOCE after re-addition of extracellular Ca^{2+}. Lower panel: Enhanced basal Ca^{2+} levels may activate PKC, inhibit IP_3-induced store release and attenuate receptor-mediated activation of K^+ channels, thus inducing basal transcription of IL-6. In renal tubules, ANO9 is predominantly expressed in the PM of the brush boarder, where it may interact with the scaffold DLG1, potentially activating PMCA.

12. ANO9

Scramblase activity has also been suggested for ANO9, which operates as a cAMP/PKA and Ca^{2+}-activated cation channel permeable for Ca^{2+} [21,62,98,107,108]. ANO9 is expressed in the plasma membrane of olfactory epithelium allowing Ca^{2+} influx from the extracellular space thereby amplifying olfactory signals initiated by activation of cyclic nucleotide-gated channels [108]. We detected low level expression of ANO9 in the ER of isolated renal epithelial cells where it could operate as a Ca^{2+} leak or counterion channel. More recent data indicate a location of ANO9 in the brush boarder membrane of proximal tubular epithelial cells (Schreiber et al., in this issue of *Cell Calcium*). Earlier data and own unpublished results suggest that ANO3,4,5,9 are activated at $[Ca^{2+}]i$ of 1 μM [26]. Due to various Ca^{2+} leakage channels, the ER membrane has a permanent background permeability for Ca^{2+} [109], which is constantly balanced by SERCA-mediated reuptake of Ca^{2+} back into the ER. Due to these circumstances Ca^{2+} concentrations near the cytoplasmic ER membrane are probably enhanced and are sufficient to activate ER-localized anoctamins. In ANO9-overexpressing cells, Ca^{2+} leakage may reduce ER Ca^{2+} content and could contribute to enhanced basal cytosolic Ca^{2+} levels, thereby enhancing the activity of PMCA. Enhanced basal Ca^{2+} levels in ANO9-expressing cells may activate PKC and inhibit IP_3R, thereby attenuating IP_3-induced release of Ca^{2+} and counteracting receptor-mediated activation of Ca^{2+}-regulated K^+ channels. In parallel basal transcription of IL-6 was found to be enhanced [42,43,98,110]. In renal tubules, ANO9 is predominantly expressed in brush boarder membranes and interacts with the scaffold Discs Large Homolog 1 (DLG1), which potentially activates PMCA (own unpublished data). The ANO9 variant T604A is associated with chronic kidney disease, as detected in a large GWAS meta-analysis [111]. Interestingly, polymorphisms in a genomic region containing SIGIRR (Single Immunoglobulin Interleukin-1 Related Receptor), ANO9, and PKP3 (plakophilin 3) are associated with various types of hyperinflammatory diseases [112,113]. SIGIRR acts as a negative regulator of TLR (Toll-like receptor) and IL-1 receptor signaling, while ANO9 regulates cellular Ca^{2+} homeostasis thereby determining the level of cytokine release [98,114] (Fig. 3). Finally, ANO9 is associated with different types of cancer [115–117]. A physical association of upregulated ANO9 with epidermal growth factor receptor (EGFR) has been suggested as the cause for ANO9-induced cell proliferation. In addition, disturbed intracellular Ca^{2+} signaling in the presence of upregulated ANO9 should also be considered as a possible mechanism for tumor growth. Similarly, overexpression of ANO1 also enhances basal Ca^{2+} levels, strongly augments proliferation and promotes development of cancer [5,118,119].

13. ANO10

ANO10 is an ER-localized intracellular Ca^{2+}-activated scramblase that redistributes PtdSer between both ER membrane leaflets [9,63]. Possibly by this mechanism it can regulate endosomal sorting [30].

Mutations of ANO10 impair neuromuscular function and cause spinocerebellar ataxia. Proteomic mapping of ANO10 identified interactions with ER proteins, the proteasome, the nuclear membrane, endosomal proteins and mitotic spindles [30,120]. We found that removal of ANO10 impairs intracellular Ca^{2+} signaling, causing defective ion transport and reduced volume regulation [19]. Cell cycle dependent colocalization of Ano10 with acetylated tubulin, centrioles, and submembraneous tubulin was detected. Along these studies, the spindle-associated transmembrane ortholog of ANO10, Axs, is known in Drosophila for its role in mitotic spindle formation, association with the ER, and Ca^{2+} signaling. [121,122]. Intestinal epithelial cells from Ano10 null mice are reduced in size and lack of spontaneous and TNFα-induced apoptosis. Moreover, a missense variant of ANO10 is associated with spinocerebellar ataxia and was shown to impair immune defense against Borrelia infection, probably due to abnormal regulation of intracellular Ca^{2+} signals in cerebellar neurons and skin macrophages [123].

14. Conclusions

Intracellular anoctamins are truly fascinating as they control a plethora of cellular functions. Abnormal expression and genetic variations contribute to a large number of rather diverse diseases. One possible reason for the large number of different anoctamin paralogues could be their role in precise and cell-dependent regulation of intracellular Ca^{2+} signaling. ER-localized anoctamins may control Ca^{2+} signaling by affecting Ca^{2+}-store filling or compromising the function of other ER proteins [124]. Moreover, they may help to direct the ER to different MCSs via proteins like DLG1, thereby regulating store-operated Ca^{2+} influx via Orai1 [98]. Ca^{2+} activated scramblase activity of intracellular anoctamins can be detected upon overexpression and PM-targeting, with the exception of ANO8 [62]. However, it remains to be proven whether these anoctamins truly scramble PL under physiological conditions in native cells. The PM-located scramblase ANO6 requires unphysiologically high (1–10 μM) $[Ca^{2+}]i$ to be activated, while EC50 % values for Ca^{2+} activation of intracellular anoctamins are still missing. Previous data demonstrated a predominant luminal presence of PtdSer in the ER membrane [125,126], while recent data show the role of ANO10 for endosomal sorting, possibly through redistribution of PtdSer between luminal and cytoplasmic ER-leaflets [30,63]. PtdSer is the predominant anionic species in membranes, and particularly common in the PM [125,127]. The PtdSer content determines surface charge, membrane curvature and ultimately the cellular localization of proteins [126,128–130]. Ca^{2+}-dependent trafficking of intracellular organelles and cellular distribution of proteins could be therefore determined by anoctamin-mediated PL-scrambling. As the ER-content of PtdSer is low (<4 %) and mostly luminal [125], other PLs might be more relevant in this process. The role of PL scrambling for membrane fusion by the anoctamin ANO6 has been discussed here and elsewhere [130–135]. Exocytic release of mucus and lysozyme in goblet and Paneth cells, respectively, and PM-targeting of CFTR by ANO6/ANO1 are further examples for translocation of proteins by anoctamins [136–139]. As stated in the beginning of this review, the term "intracellular anoctamins" is actually misleading as ANO4, 5, and 9 have also been detected in the plasma membrane (Fig. 4). We have only just begun to examine these anoctamins, while more studies in original tissues will certainly help to decipher the function of intracellular scramblases.

CRediT authorship contribution statement

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

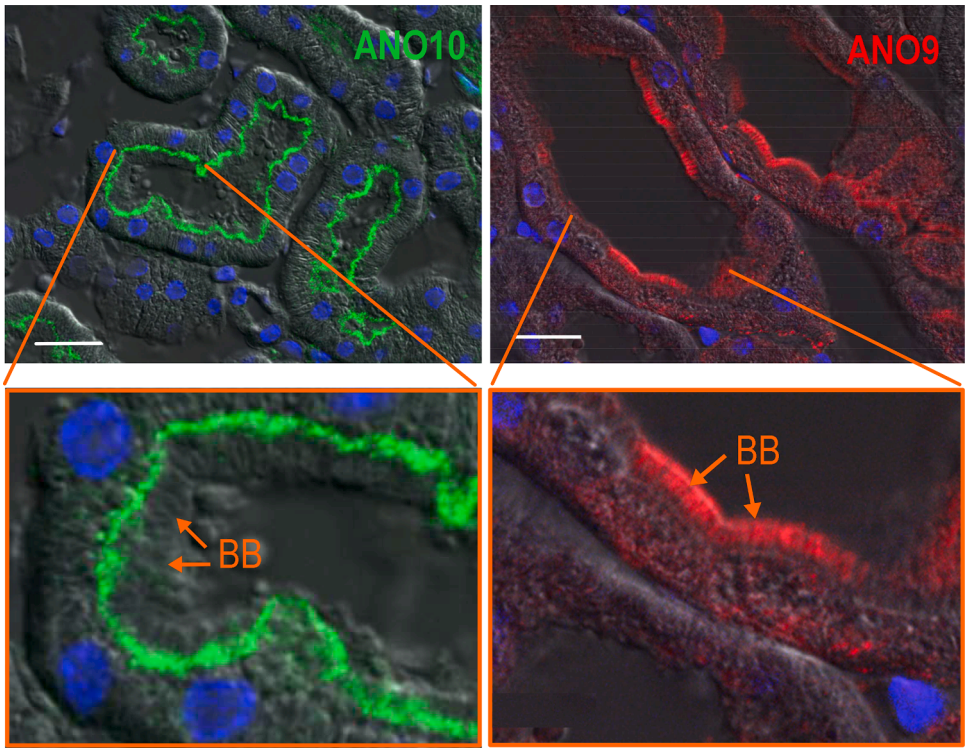


Fig. 4. Expression of intracellular anoctamins depend on cellular differentiation. In renal proximal tubular epithelium ANO10 is localized precisely under the brush boarder (BB, green staining, left panels). This corresponds to its function as a regulator of endosomal trafficking because the proximal tubule is the place where reabsorption of filtrated proteins by receptor-mediated endocytosis takes place. In contrast, ANO9 shows a weak intracellular staining and is located in the brush boarder membrane of some proximal epithelial cells (red staining, right panels). Nuclei are stained in blue by DAPI.

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.

Acknowledgment

Supported by DFG Transregio-SFB, Project-ID 509149993, TRR 374 (Project A3).

References

[1] N. Pedemonte, L.J. Galietta, Structure and function of TMEM16 proteins (Anoctamins), Physiol. Rev. 94 (2014) 419–459.
[2] Y. Tian, P. Kongsuphol, M.J. Hug, J. Ousingsawat, R. Witzgall, R. Schreiber, K. Kunzelmann, Calmodulin-dependent activation of the epithelial calcium-dependent chloride channel TMEM16A, FASEB J. 25 (2011) 1058–1068.
[3] Y. Tian, R. Schreiber, K. Kunzelmann, Anoctamins are a family of Ca2+ activated Cl- channels, J. Cell Sci. 125 (2012) 4991–4998.
[4] R. Schreiber, I. Uliyakina, P. Kongsuphol, R. Warth, M. Mirza, J.R. Martins, K. Kunzelmann, Expression and function of epithelial anoctamins, J. Biol. Chem 285 (2010) 7838–7845.
[5] I. Cabrita, R. Benedetto, A. Fonseca, P. Wanitchakool, L. Sirianant, B.V. Skryabin, L.K. Schenk, H. Pavenstadt, R. Schreiber, K. Kunzelmann, Differential effects of anoctamins on intracellular calcium signals, FASEB J. 31 (2017) 2123–2134.
[6] N.S. Imjeti, S. Lebreton, S. Paladino, E. de la Fuente, A. Gonzalez, C. Zurzolo, N-Glycosylation instead of cholesterol mediates oligomerization and apical sorting of GPI-APs in FRT cells, Mol. Biol. Cell 22 (2011) 4621–4634.
[7] H. Yang, A. Kim, T. David, D. Palmer, T. Jin, J. Tien, F. Huang, T. Cheng, S. R. Coughlin, Y.N. Jan, L.Y. Jan, TMEM16F forms a Ca(2+)-activated cation channel required for lipid scrambling in platelets during blood coagulation, Cell 151 (2012) 111–122.
[8] C. Alvadia, N.K. Lim, V. Clerico Mosina, G.T. Oostergetel, R. Dutzler, C. Paulino, Cryo-EM structures and functional characterization of the murine lipid scramblase TMEM16F, Elife 8 (2019).
[9] S.R. Bushell, A.C.W. Pike, M.E. Falzone, N.J.G. Rorsman, C.M. Ta, R.A. Corey, T. D. Newport, J.C. Christianson, L.F. Scofano, C.A. Shintre, A. Tessitore, A. Chu, Q. Wang, L. Shrestha, S.M.M. Mukhopadhyay, J.D. Love, N.A. Burgess-Brown, R. Sitsapesan, P.J. Stansfeld, J.T. Huiskonen, P. Tammaro, A. Accardi, E. P. Carpenter, The structural basis of lipid scrambling and inactivation in the endoplasmic reticulum scramblase TMEM16K, Nat. Commun. 10 (2019) 3956.
[10] Y. Han, Z. Zhou, R. Jin, F. Dai, Y. Ge, X. Ju, X. Ma, S. He, L. Yuan, Y. Wang, W. Yang, X. Yue, Z. Chen, Y. Sun, B. Corry, C.D. Cox, Y. Zhang, Mechanical activation opens a lipid-lined pore in OSCA ion channels, Nature (2024) in press.
[11] X. Yue, Y. Sheng, L. Kang, R. Xiao, Distinct functions of TMC channels: a comparative overview, Cell Mol. Life Sci. 76 (2019) 4221–4232.
[12] L. Sirianant, J. Ousingsawat, Y. Tian, R. Schreiber, K. Kunzelmann, TMC8 (EVER2) attenuates intracellular signaling by Zn2+ and Ca2+ and suppresses activation of Cl- currents, Cell Signal. 26 (2014) 2826–2833.
[13] A. Medrano-Soto, G. Moreno-Hagelsieb, D. McLaughlin, Z.S. Ye, K.J. Hendargo, M.H. Saier Jr, Bioinformatic characterization of the anoctamin superfamily of Ca2+-activated ion channels and lipid scramblases, PLoS ONE 13 (2018) e0192851.
[14] K. Li, Y. Guo, Y. Wang, R. Zhu, W. Chen, T. Cheng, X. Zhang, Y. Jia, T. Liu, W. Zhang, L.Y. Jan, Y.N. Jan, Drosophila TMEM63 and mouse TMEM63A are lysosomal mechanosensory ion channels, Nat. Cell Biol. 26 (2024) 393–403.
[15] L. Ebihara, P. Acharya, J.J. Tong, Mechanical stress modulates calcium-activated-chloride currents in differentiating lens cells, Front. Physiol. 13 (2022) 814651.
[16] A.K. Dutta, K. Woo, A.K. Khimji, C. Kresge, A.P. Feranchak, Mechanosensitive Cl-secretion in biliary epithelium mediated through TMEM16A, Am. J. Physiol. Gastrointest. Liver Physiol. 304 (2012) G87–G98.
[17] J. Almaca, Y. Tian, F. AlDehni, J. Ousingsawat, P. Kongsuphol, J.R. Rock, B. D. Harfe, R. Schreiber, K. Kunzelmann, TMEM16 proteins produce volume regulated chloride currents that are reduced in mice lacking TMEM16A, J. Biol. Chem. 284 (2009) 28571–28578.
[18] L. Sirianant, J. Ousingsawat, P. Wanitchakool, R. Schreiber, K. Kunzelmann, Cellular volume regulation by anoctamin 6:Ca2+, phospholipase A2, osmosensing, Pflügers Arch. 468 (2016) 335–349.
[19] P. Wanitchakool, J. Ousingsawat, L. Sirianant, I. Cabrita, D. Faria, R. Schreiber, K. Kunzelmann, Cellular defects by deletion of ANO10 are due to deregulated local calcium signaling, Cell Signal. 30 (2017) 41–49.
[20] G. Khelashvili, A.K. Menon, Phospholipid scrambling by G protein-coupled receptors, Annu. Rev. Biophys. 51 (2022) 39–61.
[21] J. Suzuki, T. Fujii, T. Imao, K. Ishihara, H. Kuba, S. Nagata, Calcium-dependent phospholipid scramblase activity of TMEM16 family members, J. Biol. Chem. 288 (2013) 13305–13316.
[22] H. Kim, E. Kim, B. Lee, Investigation of phosphatidylserine-transporting activity of human TMEM16C isoforms, Membranes 12 (2022) 1005.
[23] J. Ousingsawat, K. Talbi, H. Gómez-Martín, A. Koy, A. Fernández-Jaén, H. Tekgül, E. Serdaroğlu, R. Schreiber, J.D. Ortigoza-Escobar, K. Kunzelmann, Broadening the clinical spectrum: molecular mechanisms and new phenotypes of ANO3-dystonia, Brain (2023).
[24] J.M. Whitlock, K. Yu, Y.Y. Cui, H.C. Hartzell, Anoctamin 5/TMEM16E facilitates muscle precursor cell fusion, J. Gen. Physiol. 150 (2018) 1498–1509.
[25] J.R. Martins, D. Faria, P. Kongsuphol, B. Reisch, R. Schreiber, K. Kunzelmann, Anoctamin 6 is an essential component of the outwardly rectifying chloride channel, Proc. Natl. Acad. Sci. U. S. A 108 (2011) 18168–18172.
[26] R. Schreiber, J. Ousingsawat, K. Kunzelmann, Targeting of intracellular TMEM16 proteins to the plasma membrane and activation by purinergic signaling, Int. J. Mol. Sci. 21 (2020) 4065.
[27] J. Suzuki, M. Umeda, P.J. Sims, S. Nagata, Calcium-dependent phospholipid scrambling by TMEM16F, Nature 468 (2010) 834–838.
[28] T. Shimizu, T. Iehara, K. Sato, T. Fujii, H. Sakai, Y. Okada, TMEM16F is a component of a Ca2+-activated Cl- channel but not a volume-sensitive outwardly rectifying Cl- channel, Am. J. Physiol. Cell Physiol. 304 (2013) C748–C759.
[29] J. Ousingsawat, P. Wanitchakool, A. Kmit, A.M. Romao, W. Jantarajit, S. Schreiber, K. Kunzelmann, Anoctamin 6 mediates effects essential for innate immunity downstream of P2×7-receptors in macrophages, Nat. Commun. 6 (2015) 6245.
[30] M. Petkovic, J. Oses-Prieto, A. Burlingame, L.Y. Jan, Y.N. Jan, TMEM16K is an interorganelle regulator of endosomal sorting, Nat. Commun. 11 (2020) 3298.
[31] C. Duran, Z. Qu, A.O. Osunkoya, Y. Cui, H.C. Hartzell, ANOs 3-7 in the anoctamin/tmem16 Cl- channel family are intracellular proteins, Am. J. Physiol. Cell Physiol. 302 (2011) C482–C493.
[32] L.M. Lange, J. Junker, S. Loens, H. Baumann, L. Olschewski, S. Schaake, H. Madoev, S. Petkovic, N. Kuhnke, M. Kasten, A. Westenberger, A. Domingo, C. Marras, I.R. König, S. Camargos, L.J. Ozelius, C. Klein, K. Lohmann, Genotype-phenotype relations for isolated dystonia genes: MDSGene systematic review, Mov. Disord. 36 (2021) 1086–1103.
[33] J.P. Miller, H.J. Moldenhauer, S. Keros, A.L. Meredith, An emerging spectrum of variants and clinical features in KCNMA1-linked channelopathy, Channels (Austin) 15 (2021) 447–464.
[34] G. Zhang, R.A. Gibson, M. McDonald, P. Liang, P.W. Kang, J. Shi, H. Yang, J. Cui, M.A. Mikati, A gain-of-function mutation in KCNMA1 causes dystonia spells controlled with stimulant therapy, Mov. Disord. 35 (2020) 1868–1873.
[35] F.W. Hopf, T. Seif, M.L. Mohamedi, B.T. Chen, A. Bonci, The small-conductance calcium-activated potassium channel is a key modulator of firing and long-term depression in the dorsal striatum, Eur. J. Neurosci. 31 (2010) 1946–1959.
[36] C. Mourre, C. Manrique, J. Camon, S. Aidi-Knani, T. Deltheil, N. Turle-Lorenzo, G. Guiraudie-Capraz, M. Amalric, Changes in SK channel expression in the basal ganglia after partial nigrostriatal dopamine lesions in rats: functional consequences, Neuropharmacology 113 (2017) 519–532.
[37] C. Vilchis, J. Bargas, G.X. Ayala, E. Galván, E. Galarraga, Ca2+ channels that activate Ca2+-dependent K+ currents in neostriatal neurons, Neuroscience 95 (2000) 745–752.
[38] B. Balint, R. Guerreiro, S. Carmona, N. Dehghani, A. Latorre, C. Cordivari, K. P. Bhatia, J. Bras, KCNN2 mutation in autosomal-dominant tremulous myoclonus-dystonia, Eur. J. Neurol. 27 (2020) 1471–1477.
[39] J.D. Engbers, D. Anderson, H. Asmara, R. Rehak, W.H. Mehaffey, S. Hameed, B. E. McKay, M. Kruskic, G.W. Zamponi, R.W. Turner, Intermediate conductance calcium-activated potassium channels modulate summation of parallel fiber input in cerebellar Purkinje cells, Proc. Natl. Acad. Sci. U.S.A. 109 (2012) 2601–2606.
[40] E. Coppi, F. Pedata, A.J. Gibb, P2Y1 receptor modulation of Ca2+-activated K+ currents in medium-sized neurons from neonatal rat striatal slices, J. Neurophysiol. 107 (2012) 1009–1021.
[41] Y. Yanovsky, W. Zhang, U. Misgeld, Two pathways for the activation of small-conductance potassium channels in neurons of substantia nigra pars reticulata, Neuroscience 136 (2005) 1027–1036.
[42] E.A. Finch, T.J. Turner, S.M. Goldin, Calcium as a coagonist of inositol 1,4,5-trisphosphate-induced calcium release, Science 252 (1991) 443–446.
[43] J. Gromada, T.D. Jørgensen, S. Dissing, Role of protein kinase C in the regulation of inositol phosphate production and Ca2+ mobilization evoked by ATP and acetylcholine in rat lacrimal acini, Pflugers Arch. 429 (1995) 578–586.
[44] G. Sahu, R.W. Turner, The molecular basis for the calcium-dependent slow afterhyperpolarization in CA1 hippocampal pyramidal neurons, Front. Physiol. 12 (2021) 759707.
[45] N. Helassa, S.V. Antonyuk, L.Y. Lian, L.P. Haynes, R.D. Burgoyne, Biophysical and functional characterization of hippocalcin mutants responsible for human dystonia, Hum. Mol. Genet. 26 (2017) 2426–2435.
[46] A. Domingo, R. Erro, K. Lohmann, Novel dystonia genes: clues on disease mechanisms and the complexities of high-throughput sequencing, Mov. Disord. 31 (2016) 471–477.
[47] M. Thomsen, L.M. Lange, M. Zech, K. Lohmann, Genetics and Pathogenesis of Dystonia, Annu. Rev. Pathol. 19 (2023) 99–131.
[48] F. Huang, X. Wang, E.M. Ostertag, T. Nuwal, B. Huang, Y.N. Jan, A.I. Basbaum, L. Y. Jan, TMEM16C facilitates Na(+)-activated K(+) currents in rat sensory neurons and regulates pain processing, Nat. Neurosci. 16 (2013) 1284–1290.
[49] Y. Li, L. Zhang, J. Li, C. Wang, Y. Chen, Y. Yuan, K. Xie, G. Wang, Y. Yu, A role for transmembrane protein 16C/slack impairment in excitatory nociceptive synaptic plasticity in the pathogenesis of remifentanil-induced hyperalgesia in rats, Neurosci. Bull. 37 (2021) 669–683.

[50] T.A. Wang, C. Chen, F. Huang, S. Feng, J. Tien, J.M. Braz, A.I. Basbaum, Y.N. Jan, L.Y. Jan, TMEM16C is involved in thermoregulation and protects rodent pups from febrile seizures, Proc. Natl. Acad. Sci. U.S.A. 118 (2021) e2023342118.
[51] B. Feenstra, B. Pasternak, F. Geller, L. Carstensen, T. Wang, F. Huang, J.L. Eitson, M.V. Hollegaard, H. Svanstrom, M. Vestergaard, D.M. Hougaard, J.W. Schoggins, L.Y. Jan, M. Melbye, A. Hviid, Common variants associated with general and MMR vaccine-related febrile seizures, Nat. Genet. 46 (2014) 1274–1282.
[52] L. Skotte, J. Fadista, J. Bybjerg-Grauholm, V. Appadurai, M.S. Hildebrand, T. F. Hansen, K. Banasik, J. Grove, C. Albiñana, F. Geller, C.F. Bjurström, B. J. Vilhjálmsson, M. Coleman, J.A. Damiano, R. Burgess, I.E. Scheffer, O.B. V. Pedersen, C. Erikstrup, D. Westergaard, K.R. Nielsen, E. Sørensen, M.T. Bruun, X. Liu, H. Hjalgrim, T.H. Pers, P.B. Mortensen, O. Mors, M. Nordentoft, J. W. Dreier, A.D. Børglum, J. Christensen, D.M. Hougaard, A. Buil, A. Hviid, M. Melbye, H. Ullum, S.F. Berkovic, T. Werge, B. Feenstra, Genome-wide association study of febrile seizures implicates fever response and neuronal excitability genes, Brain 145 (2022) 555–568.
[53] C. Ran, C. Fourier, D. Arafa, F. Liesecke, C. Sjöstrand, E. Waldenlind, A. Steinberg, A.C. Belin, Anoctamin 3: a possible link between cluster headache and Ca(2+) signaling, Brain Sci. 9 (2019) 184.
[54] S. Koya Kutty, E. Mulroy, F. Magrinelli, G. Di Lazzaro, A. Latorre, K.P. Bhatia, Huntington disease-like phenotype in a patient with ANO3 mutation, Parkinsonism Relat. Disord. 90 (2021) 120–122.
[55] V. Klück, C.K. Boahen, B. Kischkel, J.C. Dos Santos, V. Matzaraki, C.G. Boer, J.B. J. van Meurs, K. Schraa, H. Lemmers, H. Dijkstra, M.P. Leask, T.R. Merriman, T. O. Crişan, G.M. McCarthy, V. Kumar, L.A.B. Joosten, A functional genomics approach reveals suggestive quantitative trait loci associated with combined TLR4 and BCP crystal-induced inflammation and osteoarthritis, Osteoarthritis Cartilage 31 (2023) 1022–1034.
[56] M.H. Dizier, P. Margaritte-Jeannin, A.M. Madore, J. Esparza-Gordillo, M. Moffatt, E. Corda, F. Monier, M. Guilloud-Bataille, A. Franke, S. Weidinger, I. Annesi-Maesano, J. Just, I. Pin, F. Kauffmann, W. Cookson, Y.A. Lee, C. Laprise, M. Lathrop, E. Bouzigon, F. Demenais, The ANO3/MUC15 locus is associated with eczema in families ascertained through asthma, J. Allergy Clin. Immunol. 129 (2012) 1547–1553.
[57] J. Ousingsawat, P. Wanitchakool, R. Schreiber, M. Wuelling, A. Vortkamp, K. Kunzelmann, Anoctamin 6 controls bone mineralization by activating the calcium transporter NCX1, J. Biol. Chem. 290 (2015) 6270–6280.
[58] R. Schreiber, J. Ousingsawat, P. Wanitchakool, L. Sirianant, R. Benedetto, K. Reiss, K. Kunzelmann, Regulation of TMEM16A/ANO1 and TMEM16F/ANO6 ion currents and phospholipid scrambling by Ca2+ and plasma membrane lipid, J. Physiol. (London) 596 (2018) 217–229.
[59] P. Scudieri, E. Caci, A. Venturini, E. Sondo, G. Pianigiani, C. Marchetti, R. Ravazzolo, F. Pagani, L.J. Galietta, Ion channel and lipid scramblase activity associated with expression of tmem16F/ANO6 isoforms, J. Physiol. 593 (2015) 3829–3848.
[60] S. Grubb, K.A. Poulsen, C.A. Juul, T. Kyed, T.K. Klausen, E.H. Larsen, E. K. Hoffmann, TMEM16F (Anoctamin 6), an anion channel of delayed Ca2+ activation, J. Gen. Physiol. 141 (2013) 585–600.
[61] N. Reichhart, S. Schoberl, S. Keckeis, A.S. Alfaar, C. Roubeix, M. Cordes, S. Crespo-Garcia, A. Haeckel, N. Kociok, R. Fockler, G. Fels, A. Mataruga, R. Rauh, V.M. Milenkovic, K. Zuhlke, E. Klussmann, E. Schellenberger, O. Strauss, Anoctamin-4 is a bona fide Ca(2+)-dependent non-selective cation channel, Sci. Rep. 9 (2019) 2257.
[62] S. Gyobu, K. Ishihara, J. Suzuki, K. Segawa, S. Nagata, Characterization of the scrambling domain of the TMEM16 family, Proc. Natl. Acad. Sci. U.S.A. 114 (2017) 6274–6279.
[63] T. Tsuji, J. Cheng, T. Tatematsu, A. Ebata, H. Kamikawa, A. Fujita, S. Gyobu, K. Segawa, H. Arai, T. Taguchi, S. Nagata, T. Fujimoto, Predominant localization of phosphatidylserine at the cytoplasmic leaflet of the ER, and its TMEM16K-dependent redistribution, Proc. Natl. Acad. Sci. U.S.A. 116 (2019) 13368–13373.
[64] R. Barro Soria, F. AlDehni, J. Almaca, R. Witzgall, R. Schreiber, K. Kunzelmann, ER localized bestrophin1 acts as a counter-ion channel to activate Ca2+ dependent ion channels TMEM16A and SK4, Pflügers Arch. 459 (2009) 485–497.
[65] K. Kunzelmann, I. Cabrita, P. Wanitchakool, J. Ousingsawat, L. Sirianant, R. Benedetto, R. Schreiber, Modulating Ca2+signals: a common theme for TMEM16, Ist2, and TMC, Pflügers Arch. 468 (2016) 475–490.
[66] S. Leitzke, J. Seidel, B. Ahrens, R. Schreiber, K. Kunzelmann, M. Sperrhacke, S. Bhakdi, K. Reiss, Influence of anoctamin-4 and -9 on ADAM10 and ADAM17 sheddase function, Membranes 12 (2022) 123.
[67] C. Maniero, P. Scudieri, L. Haris Shaikh, W. Zhao, M. Gurnell, L.J.V. Galietta, M. J. Brown, ANO4 (Anoctamin 4) Is a novel marker of zona glomerulosa that regulates stimulated aldosterone secretion, Hypertension 74 (2019) 1152–1159.
[68] L. Tu, J.C. Bean, Y. He, H. Liu, M. Yu, H. Liu, N. Zhang, N. Yin, J. Han, N. A. Scarcelli, K.M. Conde, M. Wang, Y. Li, B. Feng, P. Gao, Z.L. Cai, M. Fukuda, M. Xue, Q. Tong, Y. Yang, L. Liao, J. Xu, C. Wang, Y. He, Y. Xu, Anoctamin 4 channel currents activate glucose-inhibited neurons in the mouse ventromedial hypothalamus during hypoglycemia, J. Clin. Invest. 133 (2023) e163391.
[69] Y. He, P. Xu, C. Wang, Y. Xia, M. Yu, Y. Yang, K. Yu, X. Cai, N. Qu, K. Saito, J. Wang, I. Hyseni, M. Robertson, B. Piyarathna, M. Gao, S.A. Khan, F. Liu, R. Chen, C. Coarfa, Z. Zhao, Q. Tong, Z. Sun, Y. Xu, Estrogen receptor-α expressing neurons in the ventrolateral VMH regulate glucose balance, Nat. Commun. 11 (2020) 2165.
[70] P. Akbari, A. Gilani, O. Sosina, J.A. Kosmicki, L. Khrimian, Y.Y. Fang, T. Persaud, V. Garcia, D. Sun, A. Li, J. Mbatchou, A.E. Locke, C. Benner, N. Verweij, N. Lin, S. Hossain, K. Agostinucci, J.V. Pascale, E. Dirice, M. Dunn, W.E. Kraus, S. H. Shah, Y.I. Chen, J.I. Rotter, D.J. Rader, O. Melander, C.D. Still, T. Mirshahi, D. J. Carey, J. Berumen-Campos, P. Kuri-Morales, J. Alegre-Díaz, J.M. Torres, J. R. Emberson, R. Collins, S. Balasubramanian, A. Hawes, M. Jones, B. Zambrowicz, A.J. Murphy, C. Paulding, G. Coppola, J.D. Overton, J.G. Reid, A.R. Shuldiner, M. Cantor, H.M. Kang, G.R. Abecasis, K. Karalis, A.N. Economides, J. Marchini, G. D. Yancopoulos, M.W. Sleeman, J. Altarejos, G.D. Gatta, R. Tapia-Conyer, M. L. Schwartzman, A. Baras, M.A.R. Ferreira, L.A. Lotta, Sequencing of 640,000 exomes identifies GPR75 variants associated with protection from obesity, Science 373 (2021) eabf8683.
[71] K. Kweon, E.S. Shin, K.J. Park, J.K. Lee, Y. Joo, H.W. Kim, Genome-wide analysis reveals four novel loci for attention-deficit hyperactivity disorder in Korean youths, Soa–ch'ongsonyon chongsin uihak = J. Child Adolesc. Psychiatry 29 (2018) 62–72.
[72] D.A.E. Hendrickx, J. van Scheppingen, M. van der Poel, K. Bossers, K. G. Schuurman, C.G. van Eden, E.M. Hol, J. Hamann, I. Huitinga, Gene expression profiling of multiple sclerosis pathology identifies early patterns of demyelination surrounding chronic active lesions, Front. Immunol. 8 (2017) 1810.
[73] A. de Bruyn, F. Montagnese, S. Holm-Yildiz, N. Scharff Poulsen, T. Stojkovic, A. Behin, J. Palmio, M. Jokela, J.L. De Bleecker, M. de Visser, A.J. van der Kooi, L. Ten Dam, C. Domínguez González, L. Maggi, A. Gallone, A. Kostera-Pruszczyk, A. Macias, A. Łusakowska, V. Nedkova, M. Olive, R. Álvarez-Velasco, J. Wanschitz, C. Paradas, F. Mavillard, G. Querin, G. Fernández-Eulate, R. Quinlivan, M.C. Walter, C.E. Depuydt, B. Udd, J. Vissing, B. Schoser, K. G. Claeys, Anoctamin-5 related muscle disease: clinical and genetic findings in a large European cohort, Brain 146 (2023) 3800–3815.
[74] P. Soontrapa, T. Liewluck, Anoctamin 5 (ANO5) muscle disorders: a narrative review, Genes 13 (2022) 1736.
[75] E. Di Zanni, A. Gradogna, J. Scholz-Starke, A. Boccaccio, Gain of function of TMEM16E/ANO5 scrambling activity caused by a mutation associated with gnathodiaphyseal dysplasia, Cell Mol. Life Sci. 75 (2018) 1657–1670.
[76] U. Proske, D.L. Morgan, Muscle damage from eccentric exercise: mechanism, mechanical signs, adaptation and clinical applications, J. Physiol. 537 (2001) 333–345.
[77] D.A. Griffin, R.W. Johnson, J.M. Whitlock, E.R. Pozsgai, K.N. Heller, W.E. Grose, W.D. Arnold, Z. Sahenk, H.C. Hartzell, L.R. Rodino-Klapac, Defective membrane fusion and repair in Anoctamin5 -deficient muscular dystrophy, Hum. Mol. Genet. (2016) ddw063.
[78] G. Chandra, S.C. Sreetama, D.A.G. Mázala, K. Charton, J.H. VanderMeulen, I. Richard, J.K. Jaiswal, Endoplasmic reticulum maintains ion homeostasis required for plasma membrane repair, J. Cell Biol. (2021) 220.
[79] G. Chandra, D.A.G. Mázala, J.K. Jaiswal, Coping with the calcium overload caused by cell injury: ER to the rescue, Cell Stress. 5 (2021) 73–75.
[80] N.S. Pollock, M.E. Kargacin, G.J. Kargacin, Chloride channel blockers inhibit Ca2 + uptake by the smooth muscle sarcoplasmic reticulum, Biophys. J. 75 (1998) 1759–1766.
[81] J.I. Kourie, ATP-sensitive voltage- and calcium-dependent chloride channels in sarcoplasmic reticulum vesicles from rabbit skeletal muscle, J. Membr. Biol 157 (1997) 39–51.
[82] M. Yazawa, C. Ferrante, J. Feng, K. Mio, T. Ogura, M. Zhang, P.H. Lin, Z. Pan, S. Komazaki, K. Kato, M. Nishi, X. Zhao, N. Weisleder, C. Sato, J. Ma, H. Takeshima, TRIC channels are essential for Ca2+ handling in intracellular stores, Nature 448 (2007) 78–82.
[83] J.R. Martins, P. Kongsuphol, E. Sammels, S. Daimène, F. AlDehni, L. Clarke, R. Schreiber, H. DeSmedt, M.D. Amaral, K. Kunzelmann, F508del-CFTR increases intracellular Ca2+ signaling that causes enhanced calcium-dependent Cl- conductance in cystic fibrosis, Biochim. Biophys. Acta 1812 (2011) 1385–1392.
[84] E. Venturi, R. Sitsapesan, D. Yamazaki, H. Takeshima, TRIC channels supporting efficient Ca(2+) release from intracellular stores, Pflugers Arch. 465 (2013) 187–195.
[85] S.J. Foltz, Y.Y. Cui, H.J. Choo, H.C. Hartzell, ANO5 ensures trafficking of annexins in wounded myofibers, J. Cell Biol. 220 (2021) e202007059.
[86] H. Kajiya, Calcium signaling in osteoclast differentiation and bone resorption, Adv. Exp. Med. Biol. 740 (2012) 917–932.
[87] X. Li, L. Wang, H. Wang, A. Qin, X. Qin, Ano5 modulates calcium signaling during bone homeostasis in gnathodiaphyseal dysplasia, NPJ Genom. Med. 7 (2022) 48.
[88] A.A. Baig, E.J. Haining, E. Geuss, S. Beck, F. Swieringa, P. Wanitchakool, M. K. Schuhmann, D. Stegner, K. Kunzelmann, C. Kleinschnitz, J.W. Heemskerk, A. Braun, B. Nieswandt, TMEM16F-mediated platelet membrane phospholipid scrambling is critical for hemostasis and thrombosis but not thromboinflammation in mice, Arterioscler. Thromb. Vasc. Biol. 36 (2016) 2152–2157.
[89] A.A. Schmaier, P.F. Anderson, S.M. Chen, E. El-Darzi, I. Aivasovsky, M. P. Kaushik, K.D. Sack, H.C. Hartzell, S.M. Parikh, R. Flaumenhaft, S. Schulman, TMEM16E regulates endothelial cell procoagulant activity and thrombosis, J. Clin. Invest. 133 (2023) e163808.
[90] S. Gyobu, H. Miyata, M. Ikawa, D. Yamazaki, H. Takeshima, J. Suzuki, S. Nagata, A role of TMEM16E carrying a scrambling domain in sperm motility, Mol. Cell. Biol. 36 (2015) 645–659.
[91] J. Guo, D. Wang, Y. Dong, X. Gao, H. Tong, W. Liu, L. Zhang, M. Sun, ANO7: insights into topology, function, and potential applications as a biomarker and immunotherapy target, Tissue Cell 72 (2021) 101546.
[92] S. Das, Y. Hahn, D.A. Walker, S. Nagata, M.C. Willingham, D.M. Peehl, T.K. Bera, B. Lee, I. Pastan, Topology of NGEP, a prostate-specific cell:cell junction protein widely expressed in many cancers of different grade level, Cancer Res. 68 (2008) 6306–6312.

[93] E. Kaikkonen, A. Takala, J.P. Pursiheimo, G. Wahlstrom, J. Schleutker, The interactome of the prostate-specific protein Anoctamin 7, Cancer Biomark. 28 (2020) 91–100.

[94] A. Jha, W.Y. Chung, L. Vachel, J. Maleth, S. Lake, G. Zhang, M. Ahuja, S. Muallem, Anoctamin 8 tethers endoplasmic reticulum and plasma membrane for assembly of Ca(2+) signaling complexes at the ER/PM compartment, EMBO J. 38 (2020) e101452.

[95] S. McLaughlin, D. Murray, Plasma membrane phosphoinositide organization by protein electrostatics, Nature 438 (2005) 605–611.

[96] S. Muallem, W.Y. Chung, A. Jha, M. Ahuja, Lipids at membrane contact sites: cell signaling and ion transport, EMBO Rep. 18 (2017) 1893–1904.

[97] M.F. Ritchie, E. Samakai, J. Soboloff, STIM1 is required for attenuation of PMCA-mediated Ca2+ clearance during T-cell activation, EMBO J. 31 (2012) 1123–1133.

[98] R. Schreiber, K. Talbi, J. Ousingsawat, K. Kunzelmann, A TMEM16J variant leads to dysregulated cytosolic calcium which may lead to renal disease, FASEB J. 37 (2023) e22683.

[99] F. Giordano, Y. Saheki, O. Idevall-Hagren, S.F. Colombo, M. Pirruccello, I. Milosevic, E.O. Gracheva, S.N. Bagriantsev, N. Borgese, P. De Camilli, PI(4,5)P (2)-dependent and Ca(2+)-regulated ER-PM interactions mediated by the extended synaptotagmins, Cell 153 (2013) 1494–1509.

[100] W.M. Henne, J. Liou, S.D. Emr, Molecular mechanisms of inter-organelle ER-PM contact sites, Curr. Opin. Cell Biol. 35 (2015) 123–130.

[101] O. Idevall-Hagren, A. Lü, B. Xie, P. De Camilli, Triggered Ca2+ influx is required for extended synaptotagmin 1-induced ER-plasma membrane tethering, EMBO J. 34 (2015) 2291–2305.

[102] X. Jin, S. Shah, Y. Liu, H. Zhang, M. Lees, Z. Fu, J.D. Lippiat, D.J. Beech, A. Sivaprasadarao, S.A. Baldwin, H. Zhang, N. Gamper, Activation of the Cl-channel ANO1 by localized calcium signals in nociceptive sensory neurons requires coupling with the IP3 receptor, Sci. Signal. 6 (2013) ra73.

[103] J.R. Lerias, M.C. Pinto, H.M. Botelho, N.T. Awatade, M.C. Quaresma, I.A.L. Silva, P. Wanitchakool, R. Schreiber, R. Pepperkok, K. Kunzelmann, M.D. Amaral, A novel microscopy-based assay identifies extended synaptotagmin-1 (ESYT1) as a positive regulator of anoctamin 1 traffic, Biochim. Biophys. Acta 1865 (2018) 421–431.

[104] W. Nickel, M. Seedorf, Unconventional mechanisms of protein transport to the cell surface of eukaryotic cells, Annu. Rev. Cell Dev. Biol. 24 (2008) 287–308.

[105] J. Lerias, M. Pinto, R. Benedetto, R. Schreiber, M. Amaral, M. Aureli, K. Kunzelmann, Compartmentalized crosstalk of CFTR and TMEM16A (ANO1) through EPAC1 and ADCY1, Cell Signal. 44 (2018) 10–19.

[106] R.P. Iglesia, M.B. Prado, R.N. Alves, M.I.M. Escobar, C.F.L. Fernandes, A. Fortes, M. Souza, J.M. Boccacino, G. Cangiano, S.R. Soares, J.P.A. de Araújo, D.M. Tiek, A. Goenka, X. Song, J.R. Keady, B. Hu, S.Y. Cheng, M.H. Lopes, Unconventional protein secretion in brain tumors biology: enlightening the mechanisms for tumor survival and progression, Front Cell Dev. Biol. 10 (2022) 907423.

[107] H. Kim, H. Kim, J. Lee, B. Lee, H.R. Kim, J. Jung, M.O. Lee, U. Oh, Anoctamin 9/TMEM16J is a cation channel activated by cAMP/PKA signal, Cell Calcium 71 (2018) 75–85.

[108] H. Kim, H. Kim, L.T. Nguyen, T. Ha, S. Lim, K. Kim, S.H. Kim, K. Han, S.J. Hyeon, H. Ryu, Y.S. Park, S.H. Kim, I.B. Kim, G.S. Hong, S.E. Lee, Y. Choi, L.B. Cohen, U. Oh, Amplification of olfactory signals by Anoctamin 9 is important for mammalian olfaction, Prog. Neurobiol. 219 (2022) 102369.

[109] F.O. Lemos, G. Bultynck, J.B. Parys, A comprehensive overview of the complex world of the endo- and sarcoplasmic reticulum Ca(2+)-leak channels, Biochim. Biophys. Acta. Mol. Cell Res. 1868 (2021) 119020.

[110] Y. Arita, T. Kimura, Y. Ogami, H. Nawata, Phorbol ester attenuates inositol 1,4,5-trisphosphate-induced Ca2+ release in electropermeabilized rat pancreatic acini, research in experimental medicine, Z. Gesamte Exp. Med. einschliesslich experimenteller Chirurgie 192 (1992) 295–303.

[111] K.J. Stanzick, Y. Li, P. Schlosser, M. Gorski, M. Wuttke, L.F. Thomas, H. Rasheed, B.X. Rowan, S.E. Graham, B.R. Vanderweff, S.B. Patil, C. Robinson-Cohen, J. M. Gaziano, C.J. O'Donnell, C.J. Willer, S. Hallan, B.O. Åsvold, A. Gessner, A. M. Hung, C. Pattaro, A. Köttgen, K.J. Stark, I.M. Heid, T.W. Winkler, Discovery and prioritization of variants and genes for kidney function in >1.2 million individuals, Nat. Commun. 12 (2021) 4350.

[112] S.V. Mikhailova, L.V. Shcherbakova, N.I. Logvinenko, I.I. Logvinenko, M. I. Voevoda, Polymorphism of genes associated with infectious lung diseases in Northern Asian populations and in patients with community-acquired pneumonia, Vavilovskii Zhurnal Genet. Selektsii 25 (2021) 301–309.

[113] D.J. Horne, A.K. Randhawa, T.T. Chau, N.D. Bang, N.T. Yen, J.J. Farrar, S. J. Dunstan, T.R. Hawn, Common polymorphisms in the PKP3-SIGIRR-TMEM16J gene region are associated with susceptibility to tuberculosis, J. Infect. Dis. 205 (2012) 586–594.

[114] D. Wald, J. Qin, Z. Zhao, Y. Qian, M. Naramura, L. Tian, J. Towne, J.E. Sims, G. R. Stark, X. Li, SIGIRR, a negative regulator of Toll-like receptor-interleukin 1 receptor signaling, Nat. Immunol. 4 (2003) 920–927.

[115] I. Jun, H.S. Park, H. Piao, J.W. Han, M.J. An, B.G. Yun, X. Zhang, Y.H. Cha, Y. K. Shin, J.I. Yook, J. Jung, H.Y. Gee, J.S. Park, D.S. Yoon, H.C. Jeung, M.G. Lee, ANO9/TMEM16J promotes tumourigenesis via EGFR and is a novel therapeutic target for pancreatic cancer, Br. J. Cancer 117 (2017) 1798–1809.

[116] K. Kunzelmann, J. Ousingsawat, R. Benedetto, I. Cabrita, R. Schreiber, Contribution of anoctamins to cell survival and cell death, Cancers (Basel) 19 (2019) E382.

[117] K. Katsurahara, A. Shiozaki, T. Kosuga, H. Shimizu, M. Kudou, T. Arita, H. Konishi, S. Komatsu, T. Kubota, H. Fujiwara, K. Okamoto, M. Kishimoto, E. Konishi, E. Otsuji, ANO9 regulates PD-L2 expression and binding ability to PD-1 in gastric cancer, Cancer Sci. 112 (2021) 1026–1037.

[118] U. Duvvuri, D.J. Shiwarski, D. Xiao, C. Bertrand, X. Huang, R.S. Edinger, J. R. Rock, B.D. Harfe, B.J. Henson, K. Kunzelmann, R. Schreiber, R.R. Seethala, A. M. Egloff, X. Chen, V.W. Lui, J.R. Grandis, S.M. Gollin, TMEM16A, induces MAPK and contributes directly to tumorigenesis and cancer progression, Cancer Res. 72 (2012) 3270–3281.

[119] S. Guo, L. Zhang, N. Li, ANO1: more than just calcium-activated chloride channel in cancer, Front. Oncol. 12 (2022) 922838.

[120] A. Chrysanthou, A. Ververis, K. Christodoulou, ANO10 function in health and disease, Cerebellum 22 (2022) 447–467.

[121] J. Kramer, R.S. Hawley, The spindle-associated transmembrane protein Axs identifies a membranous structure ensheathing the meiotic spindle, Nat. Cell Biol. 5 (2003) 261–263.

[122] J. Kramer, R.S. Hawley, The spindle-associated transmembrane protein Axs identifies a new family of transmembrane proteins in eukaryotes, Cell Cycle 2 (2003) 174–176.

[123] C. Hammer, P. Wanitchakool, L. Sirianant, S. Papiol, M. Monnheimer, D. Faria, J. Ousingsawat, N. Schramek, C. Schmitt, G. Margos, A. Michel, P. Kraiczy, M. Pawlita, R. Schreiber, T.F. Schulz, V. Fingerle, H. Tumani, H. Ehrenreich, K. Kunzelmann, A coding variant of ANO10, affecting volume regulation of macrophages, is associated with Borrelia seropositivity, Mol. Med. 21 (2015) 26–37.

[124] A.J. Verkleij, J.A. Post, Membrane phospholipid asymmetry and signal transduction, J. Membr. Biol. 178 (2000) 1–10.

[125] J.G. Kay, G.D. Fairn, Distribution, dynamics and functional roles of phosphatidylserine within the cell, Cell Commun. Signal. 17 (2019) 126.

[126] J.G. Kay, M. Koivusalo, X. Ma, T. Wohland, S. Grinstein, Phosphatidylserine dynamics in cellular membranes, Mol. Biol. Cell 23 (2012) 2198–2212.

[127] J.E. Vance, R. Steenbergen, Metabolism and functions of phosphatidylserine, Prog. Lipid Res. 44 (2005) 207–234.

[128] P.A. Leventis, S. Grinstein, The distribution and function of phosphatidylserine in cellular membranes, Annu. Rev. Biophys. 39 (2010) 407–427.

[129] T. Yeung, G.E. Gilbert, J. Shi, J. Silvius, A. Kapus, S. Grinstein, Membrane phosphatidylserine regulates surface charge and protein localization, Science 319 (2008) 210–213.

[130] J.M. Whitlock, L.V. Chernomordik, Flagging fusion: phosphatidylserine signaling in cell-cell fusion, J. Biol. Chem. 296 (2021) 100411.

[131] C. Bricogne, M. Fine, P.M. Pereira, J. Sung, M. Tijani, Y. Wang, R. Henriques, M. K. Collins, D. Hilgemann, TMEM16F activation by Ca(2+) triggers plasma membrane expansion and directs PD-1 trafficking, Sci. Rep. 9 (2019) 619.

[132] R. Centeio, I. Cabrita, R. Schreiber, K. Kunzelmann, TMEM16A/F support exocytosis but do not inhibit Notch-mediated goblet cell metaplasia of BCi-NS1.1 human airway epithelium, Front. Physiol. 14 (2023) 1157704.

[133] L. Braga, H. Ali, I. Secco, E. Chiavacci, G. Neves, D. Goldhill, R. Penn, J. M. Jimenez-Guardeño, A.M. Ortega-Prieto, R. Bussani, A. Cannatà, G. Rizzari, C. Collesi, E. Schneider, D. Arosio, A.M. Shah, W.S. Barclay, M.H. Malim, J. Burrone, M. Giacca, Drugs that inhibit TMEM16 proteins block SARS-CoV-2 spike-induced syncytia, Nature 594 (2021) 88–93.

[134] T.W. Han, W. Ye, N.P. Bethel, M. Zubia, A. Kim, K.H. Li, A.L. Burlingame, M. Grabe, Y.N. Jan, L.Y. Jan, Chemically induced vesiculation as a platform for studying TMEM16F activity, Proc. Natl. Acad. Sci. U.S.A. 116 (2019) 1309–1318.

[135] Y. Zhang, T. Le, R. Grabau, Z. Mohseni, H. Kim, D.R. Natale, L. Feng, H. Pan, H. Yang, TMEM16F phospholipid scramblase mediates trophoblast fusion and placental development, Sci. Adv. 6 (2020) eaba0310.

[136] J.H. Park, J. Ousingsawat, I. Cabrita, R.E. Bettels, J. Große-Onnebrink, C. Schmalstieg, S. Biskup, J. Reunert, S. Rust, R. Schreiber, K. Kunzelmann, T. Marquardt, TMEM16A deficiency: a potentially fatal neonatal disease resulting from impaired chloride currents, J. Med. Genet. 58 (2020) 247–253.

[137] R. Benedetto, J. Ousingsawat, I. Cabrita, M. Pinto, J. Lerias, P. Wanitchakool, R. Schreiber, K. Kunzelmann, Plasma membrane localized TMEM16 Proteins are Indispensable for expression of CFTR, J. Mol. Med. 97 (2019) 711–722.

[138] R. Benedetto, I. Cabrita, R. Schreiber, K. Kunzelmann, TMEM16A is indispensable for basal mucus secretion in airways and intestine, FASEB J. 33 (2019) 4502–4512.

[139] R. Schreiber, I. Cabrita, K. Kunzelmann, Paneth cell secretion in vivo requires expression of Tmem16a and Tmem16f, Gastro Hep Adv. 1 (2022) 1088–1098.