Pathological role of ion channels and transporters in the development and progression of triple-negative breast cancer

Chengli Lu†, Zhiyuan Ma†, Xiaoming Cheng1, Huichao Wu2, Biguang Tuo1-3, Xuemei Liu2-3* and Taolang Li1*

Abstract
Breast cancer (BC) is the common malignancy in women; its incidence is increased each year [1], and it has become a significant threat to women’s health [2]. BC is a heterogeneous disease that can be divided into multiple molecular subtypes based on estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER-2) expression, providing important prognostic and predictive information [3]. There are four BC subtypes depending on receptor status: luminal A, luminal B, HER-2-overexpressing and triple-negative breast cancer (TNBC). Among them, TNBC is defined as ER, PR and HER-2 negative, and it tends to affect younger women (< 40 years of age); it is prone to axillary lymph node, lung, bone metastases and has a high recurrence rate [4, 5]. Lehmann et al. classified TNBC into six subtypes based on gene cluster sequence expression: basal-like 1, basal-like 2, immunomodulatory, mesenchymal, mesenchymal stem-like and luminal androgen receptor subtypes [6]. After analyzing the RNA and DNA profile of 198 TNBC tumors, Matthew et al. classified TNBC into four subtypes, including luminal androgen receptor, mesenchymal, basal-like immune-suppressed and basal-like immune-activated subtypes [7]. The two classification methods have similarities, and both provide theoretical bases for exploring targeted therapies for TNBC.

Although TNBC is the BC subtype that responds best to chemotherapy, its recurrence and metastasis rates are higher than those of other BC subtypes [8]. Furthermore, due to the lack of classic biomarkers, TNBC lacks standard treatments guided by tumor biology, and only surgery and chemotherapy are currently available as treatments [9]. Previous studies have shown that ion channels and transporters play important regulatory roles in mammary physiology and the initiation and progression of BC.

Keywords: Triple-negative breast cancer, Ion channels, Ion transporters, Pathological roles, Targeted therapy

Background
Breast cancer (BC) is the common malignancy in women; its incidence is increased each year [1], and it has become a significant threat to women’s health [2]. BC is a heterogeneous disease that can be divided into multiple molecular subtypes based on estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER-2) expression, providing important prognostic and predictive information [3]. There are four BC subtypes depending on receptor status: luminal A, luminal B, HER-2-overexpressing and triple-negative breast cancer (TNBC). Among them, TNBC is defined as ER, PR and HER-2 negative, and it tends to affect younger women (<40 years of age); it is prone to axillary lymph node, lung, bone metastases and has a high recurrence rate [4, 5]. Lehmann et al. classified TNBC into six subtypes based on gene cluster sequence expression: basal-like 1, basal-like 2, immunomodulatory, mesenchymal, mesenchymal stem-like and luminal androgen receptor subtypes [6]. After analyzing the RNA and DNA profile of 198 TNBC tumors, Matthew et al. classified TNBC into four subtypes, including luminal androgen receptor, mesenchymal, basal-like immune-suppressed and basal-like immune-activated subtypes [7]. The two classification methods have similarities, and both provide theoretical bases for exploring targeted therapies for TNBC.

Although TNBC is the BC subtype that responds best to chemotherapy, its recurrence and metastasis rates are higher than those of other BC subtypes [8]. Furthermore, due to the lack of classic biomarkers, TNBC lacks standard treatments guided by tumor biology, and only surgery and chemotherapy are currently available as treatments [9]. Previous studies have shown that ion channels and transporters play important regulatory roles in mammary physiology and the initiation and progression of BC.

© The Author(s) 2020. This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.
However, the detailed functional role of ion channels and transporters in TNBC has not been clarified and summarized. In recent studies, upregulation of Na\(^+\)/H\(^+\) exchanger 1 has been shown to promote the proliferation, migration and invasion of the TNBC cell line MDA-MB-231 [11, 12]. In addition, Ca\(^{2+}\) channels, such as mitochondrial calcium uniporter (MCU), can promote TNBC cell migration, invasion, and lung metastasis [13], and Alvarez et al. [14] reported that the two-pore domain potassium channel KCNK5 is associated with a poor prognosis in TNBC. Therefore, ion channels and transporters play important regulatory roles in the pathophysiology of TNBC, but there is currently no relevant review on this topic. Here, we review the pathological roles of ion channels and transporters, including AQPs, Cl\(^-\) channels, Ca\(^{2+}\) channels, K\(^+\) channels, and acid-base transporters, in the initiation and progression of TNBC.

**AQPs**

AQPs (which compose a family of transmembrane water channel proteins) modulate the movement of water and small solutes into and out of cells and maintain suitable concentrations of water and solutes for cell survival [15]. At least 13 AQP subtypes (AQP0-12) have been identified in mammals and are divided into two families based on transfer specificity, namely, the classic water-transporting AQP family and the solute-, water-, and glycerol-transporting glycoprotein family [16]. AQP0-2, AQP4 to AQP6-8 are mainly water-selective; AQP3, AQP7, AQP9, AQP10 and AQP12 also transport glycerol and possibly other small solutes. AQPs also play roles in the transport of ammonia, urea, carbon dioxide, metalloids, nitric oxide and certain ions [17]. Expression of AQP1, AQP3-5 and AQP10-12 has been detected in normal human mammary tissue and is closely related to milk secretion [18, 19]. In addition, deletion of “CCAAT”/enhancer binding protein (a family of transcription factors) \(\beta\) isoforms results in changes in mammary ducal morphogenesis and changes in expression of transport proteins such as AQP5, suggesting that AQP5 may be involved in mammary development [20]. Recent studies have shown that AQPs play carcinogenic roles by promoting angiogenesis, enhancing invasive and metastatic potential, and enhancing the transport of reactive oxygen species (ROS) [21, 22]. In female-specific cancers, such as BC, AQP1, 3, and 5 are the most important AQPs, and they are been reported to be upregulated [23].

AQP1, the membrane protein, was the first reported mammalian AQP and plays a significant role in tumor cell migration, proliferation and angiogenesis [24]. Clinical studies have shown that patients with TNBC have higher levels of AQP1 expression and that upregulation correlates with a poor prognosis [25, 26]. AQP1 expression is induced by hypoxia through the E-Box/ChoRE transcription element, which is affected by increased glucose consumption and metabolism [27]. AQP1 expression has been detected only in a subgroup of CK14-positive basal-like breast cancer (BLBC) cases [25]. CK14 has been used as a marker of basal mammary epithelial cells with in vivo regenerative ability in studies on mammary gland progenitor and stem cells [28]. Therefore, it is speculated that expression of AQP1 is related to the stem cell characteristics of BLBC cells. Hu et al. demonstrated that AQP1 upregulation promotes extravasation and increases migration in vivo and in vitro in the mouse TNBC cell line 4T1, suggesting that this aquaporin enhances the rate of cell migration by promoting water permeability in cell protrusions [29]. Thus, upregulation of AQP1 can promote the proliferation, migration and invasion in TNBC cells. Moreover, in vivo experiments have shown that AQP1 deficiency can reduce tumor mass, volume, vessel density and lung metastases in MMTV-PyVT (mouse mammary tumor virus-driven polyoma virus middle T oncogene) mice, and inhibition of AQP1 function and/or expression is predicted to attenuate angiogenesis via reduced migration and invasion of endothelial cells [30]. Recently, Irene Abreu-Rodriguez et al. [31] revealed that AQP1 expression is also responsive to hypoxia-inducible factor (HIF), which may play a role in the VEGF-independent signaling mechanism inducing angiogenesis in a hypoxic environment. Helen et al. [32] also reported that the triterpenoid saponins bacopside I and bacopside II can synergistically reduce the transcriptional expression of AQP1, and inhibit proliferation, migration and invasion in MDA-MB-231 cells. Similarly, ginsenoside Rg3, a compound with anticancer activity isolated from ginseng, inhibits AQP1 to attenuate cell proliferation through a mechanism that involves downregulation of AQP1 to induce cell cycle arrest in G0/G1 phase by inhibiting cyclin D and E and inhibition of chemoattractant-induced cell migration and invasion by blocking AQP1-mediated water flux in MDA-MB-231 cells [33]. These findings indicate that AQP1 plays an important role in the development and progression of TNBC.

Overexpression of AQP3 has been detected in the membranes and cytoplasm of TNBC tumor cells and is significantly associated with poor prognosis [34]. Xu-Chen Cao et al. [35] found that the presence of fibroblast growth factor-2 (FGF-2) induced cell migration and metastasis in MDA-MB-231 cells by increasing AQP3 expression. Moreover, FGF receptor kinase (FGFRK) inhibitors, PI3K inhibitors, and MEK1/2 inhibitors all inhibit AQP3 expression, suggesting that FGF receptor kinases increase AQP3 expression and promote FGF-2-induced cell migration by initiating downstream PI3K and ERK pathways. In addition, CuSO\(_4\), a water transport
inhibitor of AQP3, inhibits migration in MDA-MB-231 cells; AQP3 downregulation reduces the proliferation, invasion and migration of MDA-MB-231 cells while increasing sensitivity to 5-fluorouracil chemotherapy. The mechanism may be related to a decrease in glycerol permeability caused by AQP3 downregulation [36]. Overall, these findings demonstrate that AQP3 plays a pivotal role in the initiation and progression of TNBC, and specific inhibitors of AQP3 in clinical applications may improve the therapeutic effect of TNBC patients.

Similarly, overexpression of AQP5 in the membrane and cytoplasm of TNBC cells has been detected and is significantly associated with poor prognosis [34]. Moreover, patients with higher Ki-67 expression are more likely to have abnormal AQP5 protein expression than patients with lower Ki-67 expression [34]. Ki-67 is a widely accepted proliferation marker [37, 38], and it is speculated that upregulation of AQP5 may promote proliferation in TNBC cells.

In summary, AQP1, AQP3, and AQP5 are significantly upregulated in TNBC; this upregulation is related to a poor prognosis and can promote the proliferation, invasion, and migration of TNBC cells. These AQPs are promising new targets for the diagnosis and treatment of TNBC.

**Cl− channels**

**CFTR**

CFTR is a member of the ATP-binding cassette transporter family that localizes at the apical membranes of normal epithelial cells. CFTR is mainly responsible for conducting HCO3− and Cl− and promoting HCO3− secretion in many tissues, including the airway, intestines and pancreas [39]. However, when the extracellular concentration of Cl− is higher than 40 mmol/L, the permeability of CFTR to Cl− is much greater than that of CFTR to HCO3−; thus, CFTR mainly conducts Cl− under physiological conditions [40]. CFTR can also transport two other anions, glutathione and thiocyanate, which are involved in airway inflammation and oxidative stress [41, 42]. Interestingly, Pierre et al. [43] reported that CFTR is required for the tightly connected functions of normal epithelial tissues; loss of CFTR reduces epithelial resistance and epithelial integrity, and this effect is not related to the anion channel function of CFTR.

CFTR has been reported to be associated with several cancers, such as cervical cancer [44], colorectal cancer [45], prostate cancer [46] and BC [47]. Significant down-regulation of CFTR expression is observed in BC tissue compared to normal mammary tissue [48]. Zhang et al. demonstrated that overexpression of CFTR inhibits EMT, invasion and migration in MDA-MB-231 cells via a mechanism that involves CFTR inhibition of NFκB targeting of urokinase-type plasminogen activator [47].

In addition, CFTR overexpression inhibits the EMT and the invasiveness of MDA-MB-231 cells and reduces lung metastasis in xenograft models. Increasing evidence reveals that downregulation of CFTR occurs after treatment with EMT-inducing factors such as TGF-β, suggesting that as a downstream effector, CFTR plays important roles in mediating various EMT effects [49, 50]. Moreover, hypermethylation of the cancer genome leads to activation of oncogenes or suppression of tumor-suppressor genes, thereby resulting in tumorigenesis [51]. It has also been observed that the methylation level of CFTR in BC tissues is much higher than that in normal tissues, and treatment with DNA methylation inhibitors in TNBC cell lines (MDA-MB-231 and MDA-MB-435) can rescue CFTR mRNA, indicating that CFTR methylation plays an important role in TNBC [52]. ΔF508 is the most common mutation in CFTR, causing the protein to be retained and degraded in the endoplasmic reticulum due to misfolding [53]. It is worth noting that although there is no difference in the incidence of BC between ΔF508 carriers and noncarriers, patients with ΔF508 CFTR mutations all have grade III cancer, indicating that CFTR defects are associated with BC progression [54]. Therefore, CFTR methylation or mutation need to be further investigated in the future, which may provide novel therapeutic intervention for TNBC.

**Chloride channel 3**

The chloride channel (CIC) family also plays an indispensable role in the transport of Cl− [55]. There are nine family members in humans, which are divided into two categories based on their distribution and physiological function: (1) Cl− channel proteins (CIC1, CIC2, CICKa and CICKb), which mainly exist in the plasma membrane and play roles in stabilizing membrane electric potential or mediating epithelial transport; and (2) Cl−/H+ reverse transporter proteins (CIC3-7), which mainly exist in the vascular intima of the endosome-lysosomal pathway and are localized at the plasma membrane only to a limited extent due to protein degradation and hydrolase activity [56, 57]. In recent years, it has been discovered that CIC3 can transport one hydrogen ion in exchange for two chloride ions [58], with important roles in cancers such as nasopharyngeal carcinoma [59] and BC.

CIC3 overexpression is observed in tissues and the TNBC cell line MDA-MB-231 [60, 61]. Studies by Zhou et al. revealed that knockdown of CIC3 downregulates expression of cyclin D1 and cyclin E and increases levels of p21, indicating that knockdown of CIC3 can block the cell cycle of MDA-MB-231 cells at G0/G1 phase, inhibiting cell proliferation. Moreover, knockdown of CIC3 suppresses tumor growth in xenograft models and significantly reduces levels of pERK1/2 in MDA-MB-231 cells.
This indicates that CIC3 can promote the progression of TNBC by acting on the ERK1/2 signaling pathway [60]. Nevertheless, relative research on CIC3 in TNBC is still very limited, and extensive work is needed in the further.

**Ca^{2+} channels**

Ca^{2+} is a key nutrient in milk that plays a vital role in the mineralization of bones and teeth, and as a second messenger, ionized Ca^{2+} is a key regulator of proliferation, migration, cell cycle progression and apoptosis [62]. The level of Ca^{2+} is very low in the cytoplasm (~10^{-7} mol/L), whereas it is somewhat higher in organelles (~10^{-5} mol/L) and highest in the extracellular level milieu (~10^{-3} mol/L). Hence, a small amount of Ca^{2+} can significantly change intracellular levels to activate downstream signaling molecules, including calmodulin, nuclear factor of activated T-cells (NFAT), Nfkb, calmodulin-dependent protein kinase II, calpain and others [63, 64]. In nonexcitatory mammary cells, calcium channels play important roles in lactation and the maintenance of normal physiological functions [65, 66].

Continuous increases in intracellular Ca^{2+} levels will drive expression of oncogenes, resulting in tumor growth and development, especially the metastatic behavior of cancer cells, and conferring tumor cells with resistance to apoptosis [67]. Abnormal expression of several Ca^{2+} transporters and ion channels, such as calcium release-activated calcium modulator 1 (Orai1), has been observed in TNBC and may lead to oncogenic Ca^{2+} signaling [68]. Interestingly, specific changes in the expression and function of Ca^{2+} channels are related to hormone receptor status and differ significantly among BC subtypes [69].

**Calcium modulator 1**

Ca^{2+} influx mainly depends on store-operated calcium channels (SOCCs). When the Ca^{2+} concentration in the endoplasmic reticulum declines to a certain level, the STIM (stromal interaction molecule), which is located on the endoplasmic reticulum membrane, moves to a position close to the highly selective calcium channel protein Orai on the cell membrane. Subsequently, Orai is activated to cause Ca^{2+} influx, and store-operated calcium entry (SOCE) is initiated, thereby replenishing the calcium store. Some researchers have proposed that the canonical transient receptor potential (TRPC) also participates in the above process, though the mechanism remains controversial. There are two different claims: that both Orai and TRPC form independent channels activated by the STIM protein and that Orai and TRPC subunits form heterochannels triggered by STIM [70]. There are three Orai1 isomers (Orai1 to Orai3) and two STIM homologs (STIM1 and STIM2). SOCE has been found to be primarily mediated by Orai1 and STIM1 in TNBC [71]. Compared with that in nonmalignant breast epithelial cells, expression of Orai1 and STIM1 is significantly higher in TNBC cell lines and is associated with a poor prognosis [72, 73]. Liu et al. [74] reported that hypoxia can induce expression of Orai1, Notch1 and Jagged-1, and Orai1 is significantly downregulated after blockade of Notch signaling, suggesting that hypoxia can increase Orai1 expression in TNBC by activating Notch signaling (Notch1/Orai1/SOCE/NFAT4 axis). Similarly, Mognol et al. [75] found that Orai1 promotes the invasion and angiogenesis of TNBC cell lines and activates NFAT4, which can regulate genes involved in the cell cycle, apoptosis, angiogenesis and metastasis. In addition, Yang et al. [76] demonstrated that Orai1 and STIM1 promote the migration and invasion of MDA-MB-231 cells both in vivo and in vitro, and the authors proposed that these proteins may at least partially control cell migration by regulating focal adhesion turnover. Furthermore, treatment with TGF-β can reduce expression of STIM1, whereas blockade of SOCE can impair TGF-β-induced G0/G1 cell cycle arrest and inhibit the proliferation of MDA-MB-231 cells [77]. Based on the above research, Orai1 and STIM1 may be new therapeutic targets for TNBC. Indeed, some selective SOCE inhibitors have shown encouraging inhibitory effects on TNBC, but they are still only in the preclinical trial stage. For example, phemindole, a di-indole derivative, reduces SOCE by downregulating STIM1 expression, significantly inhibits the proliferation and migration of MDA-MB-231 cells, reduces the growth of solid tumors in mouse models and produces a targeted antitumor effect in TNBC [78]. In addition, Miroslava Didiasova et al. [79] revealed that elevated cell surface-associated enolase-1 (ENO-1) expression correlates with augmented MDA-MB-231 cell migratory and invasive properties. Pharmacological blockade (a selective SOCC inhibitor, NS1643) or knockdown of STIM1 or Orai1 reduces ENO-1 expression and thus in the modulation of TNBC cell migratory and invasive properties, indicated that Orai1 and STIM1 might be promising therapeutic targets for TNBC.

**Secretory pathway Ca^{2+}-ATPase**

The secretory pathway Ca^{2+} pump (SPCA) can direct Ca^{2+} and Mn^{2+} from the cytoplasm to the Golgi and post-Golgi vesicles. Two isotypes (SPCA1 and SPCA2) are known, and the distribution and function of the two differ. SPCA1 is commonly expressed in mammalian tissues; expression of SPCA2 is limited to highly absorptive and secretory epithelial cells, including mammary
and salivary gland cells [80]. SPCA1 is highly expressed in TNBC cell lines, and SPCA2 is highly expressed in cell lines of other subtypes [81]. Interestingly, based on clinical samples, Desma et al. reported SPCA1 levels to be significantly elevated in the basal subtype of BC compared with all other subtypes, and it is worth noting that changes in its expression affect posttranslational modification and transport of certain proteins important for tumor progression without significantly changing cytosolic calcium signaling; SPCA1 inhibition also decreased MDA-MB-231 cell proliferation [82]. Moreover, SPCA1 is a key regulator of insulin-like growth factor receptor (IGF1R) processing in TNBC cells and promotes the production of functional IGF1R; IGF1R activity is associated with poor prognosis, suggesting that targeting SPCA1 is an alternative IGF1R-inhibiting strategy [82, 83]. Overall, upregulation of SPCA1 may promote the initiation and progression of TNBC. The main mechanism reported to date involves SPCA1-mediated increase in functional IGF1R expression.

**Mitochondrial calcium uniporter**

Upregulation of MCU expression on the mitochondrial membrane is closely related to a poor prognosis in BC [84], miR-340 correlates negatively with the metastatic potential of TNBC cells [85]; it may directly inhibit MCU expression to reduce glycolysis and exercise capacity, and knockdown or inhibition of MCU inhibits the growth, invasion and metastasis of MDA-MB-231 cells [13]. Interestingly, Anna et al. [86] demonstrated that mitochondrial Ca\(^{2+}\) uptake is required for TNBC progression in vivo and that absorption of Ca\(^{2+}\) by mitochondria promotes the production of sustained mitochondrial reactive oxygen species, activating the HIF-1α signaling pathway and promoting tumor growth and metastasis. In addition, inhibition or silencing MCU also block serum-induced migration of MDA-MB-231 cells and reduce serum or thapsigargin-induced SOCE, suggesting that MCU promotes TNBC cell migration by regulating SOCE [87]. The above results indicate that overexpression of MCU may play an important oncogenic role in the growth, invasion and metastasis of TNBC cells. However, the precise mechanism is unclear. Other promising calcium channel targets in TNBC include TRPV6 [88]. Overall, calcium channels are promising targets for TNBC treatment, but most compounds targeting these channels are only in the preclinical trial stage. Thus, further research is needed.

**K\(^{+}\) channels**

Through the action of Na\(^{+}/K^{+}\)-ATPase, two K\(^{+}\) molecules are transported into a cell in exchange for three sodium molecules, which increases the intracellular K\(^{+}\) concentration. K\(^{+}\) channels on the cell membrane are numerous, and in humans, more than 90 genes encode major K\(^{+}\) channel subunits [89]. K\(^{+}\) channels play key roles in maintaining acid-base balance by functioning in concert with the Na\(^{+}/H^{+}\) exchanger and Na\(^{+}/K^{+}\)-ATPase [90], controlling electrical excitability of nerves and muscles, and participating in energy metabolism and other physiological processes. In addition, K\(^{+}\) channels can help regulate cell proliferation and cell cycle progression and are involved in tumorigenesis [91]. Many studies have reported dysregulated K\(^{+}\) channel expression in human cancers, including BC, astrocytic-type brain cancer and prostate cancer [92, 93]. Tumor-related K\(^{+}\) channels can be divided into four major categories according to their domain structures and activation mechanisms: (1) voltage-gated potassium channels, which are controlled by changes in membrane potential; (2) calcium-activated potassium channels, which are activated by intracellular calcium; (3) inwardly rectifying potassium channels; and (4) two-pore-domain potassium channels (K2P, KCNK) [94]. However, the carcinogenic mechanism of K\(^{+}\) channels remains rather clear. Nuria et al. [95] proposed that K\(^{+}\) channels may participate in and regulate tumor progression through permeation-related mechanisms (including changes in membrane potential, Ca\(^{2+}\) driving forces and cell volume regulation) and non-conductive mechanisms (dependent on protein-protein interactions).

The Kv11.1 channel (also known as human ether-a-go-go-related gene 1, hERG1) is not expressed in normal breast cells but is expressed in BC, with a relationship with subtype. Indeed, TNBC exhibits lower expression of Kv11.1 compared with other subtypes [96]. Olivia Crociani et al. [97] showed that the mRNA levels of Kv11.1 change throughout the cell cycle, peaking in G0/G1 phase. Moreover, Lansu et al. [98] reported that stimulation of Kv11.1 led to inhibition of proliferation in MDA-MB-231 cells and that an agonist, the diphenylurea derivative NS1643, caused a significant inhibition of cell proliferation. This phenomenon can be linked to a rapid decrease in the cyclin E2 protein level, which causes accumulation of cells in G0/G1 phase and an increase in tumor suppressor proteins and markers for cellular senescence, including p21, p16\(^{ink4a}\) and β-galactosidase activity. Therefore, Kv11.1 inhibits TNBC cell proliferation by activating a cellular senescence program [98]. Breuer et al. confirmed that NS1643 reprograms the EMT by attenuating the Wnt/β-catenin signaling pathway, inhibits cancer cell stemness, and significantly reduces the metastatic spread of breast tumors in a MDA-MB-231 mouse model [99]. Regardless, cardiotoxicity is an important limiting factor for potential therapeutic molecules acting on Kv11.1. Although the activator is well tolerated.
in BC, potential effects include tachycardia [100]. Overall, the potential benefits of Kv11.1 activators as anticancer drugs outweigh their side effects.

In addition, many other channels are altered in TNBC. For example, some K2P channels with differential expression may serve as novel molecular markers associated with TNBC. RNA-Seq analysis of K2P channels has shown that overexpression of KCNK5, KCNK9, and KCNK12 and low expression of KCNK6 and KCNK15 are related to TNBC [115]. It has been confirmed that NHE1 and NBCn1 promote the development of TNBC through different mechanisms. There are two main NHE1 inhibitors, amiloride and cariporide, which are more effective than amiloride and highly selective [116]. Amiloride is a potassium-sparing diuretic and has blocking effects on a variety of ion channels, such as NHE and the Na+/Ca2+ exchanger. Cariporide is a highly specific and powerful NHE1 inhibitor that is relatively well tolerated in humans with heart disease [117]. Moreover, a study has suggested that KR-33028, a novel small molecule inhibitor of NHE1, produces a cellular phenotype comparable to that of NHE1 knockout cells and significantly decreases rates of migration, invasion and colony growth in TNBC cell lines MDA-MB-231, MDA-MB-468 and Hs578T [118]. The above findings suggest that NHE1 may play an important role in the progression of TNBC.

Additionally, other acid-base transporters are also altered in TNBC and are expected to emerge as new targets for TNBC treatment. For instance, NBCe1 (SLC4A4) knockdown reduces cell proliferation, invasion and migration in TNBC cells expressing high levels of NBCe1 [119]. The above findings all suggest that the acid-base transporters have essential functions in the occurrence and development of TNBC, but further research is needed.

**Acid-base transporters**

The pH of milk is significantly lower than that of plasma, indicating that there may be some acid-base transporters in the mammary gland that regulate the pH between the extracellular fluid and milk [102]. A uniform feature among solid tumors with high metabolic and proliferative rates is a significantly different pH from that of normal tissue [103]. Cancer cells can maintain a weakly acidic intracellular pH that is even more alkaline than that of normal cells, suggesting that tumor cells have a powerful pH regulation system [104].

The Na+/H+ exchanger (NHE), a membrane transporter, mainly catalyzes the exchange of intracellular H+ for extracellular Na+ in mammals, thereby maintaining the pH balance inside and outside the cell [105, 106]. There are 10 subtypes of NHE, with tissue- and membrane-specific expression patterns. NHE1-5 are located on the plasma membrane, and NHE6-9 are on intracellular organelle membranes; NHE10 is only expressed in osteoclasts [107]. In addition, NHE plays indispensable roles in maintaining normal mammary structure and physiological functions [108]. NHE1 (SLC9A1) is universally expressed in epithelial cells and upregulated in BC tissues compared to normal tissues [109]. Studies have shown that hypoxia, various growth factors, and hormones, among others, can activate NHE1, and enhanced NHE1 activity can reduce extracellular pH and promote metastasis of MDA-MB-231 cells [110]. Furthermore, it has been proposed that NHE1 promotes metastasis and remodeling of the extracellular matrix by acidifying the extracellular microenvironment [111]. In addition, NHE1 knockdown reduces the migration, invasion, and growth of xenograft tumors of MDA-MB-231 cells, increasing the susceptibility of these cells to paclitaxel [112, 113]. Moreover, knockdown of NHE1 or NBCn1 (SLC4A7) in the MDA-MB-231 cell line significantly reduced the steady-state intracellular pH value after acid load, the ability to restore pHi and the primary tumor growth of xenografts in vivo, but NBCn1 knockdown prolonged tumor-free survival and reduced cell proliferation [114, 115]. The above findings indicate that K+ channels play an important role in TNBC and are expected to be diagnosis markers.

**Conclusions**

Dysfunction of ion channels and transporters in the mammary resulted in development and progression of TNBC. Despite extensive work has been performed to investigate the expression pattern, functional diversity, regulatory mechanism and pathophysiology of different ion transporters in TNBC, the systematic review is rare in this field. Therefore, this review focuses on different pathological function of multiple families in the development and progression of TBNC, including the AQP, Cl− channels, Ca2+ channels, K+ channels and acid-base transporters (Fig. 1; Table 1). We hope that we can provide a basic, systemic and summarised knowledge to this field, advocating researchers play more attention on the pathophysiological role of ion channels and transporters in the development and progression of TNBC, which may provide novel targets for the clinical diagnosis and treatment of TNBC.
Fig. 1 Pathological roles of ion channels and transporters in triple-negative breast cancer cells. Alteration and dysfunction of AQPs, Cl⁻ channels, Ca²⁺ channels, K⁺ channels, Na⁺/HCO₃⁻ transporter and Na⁺/H⁺ exchanger results in abnormality of ion transport and disorder of multiple signaling pathway, including WNT, PI3K, TGFβ, Notch and VEGF, etc., eventually promoting TNBC cell proliferation, migration and invasion, but inhibiting apoptosis. (The red boxes indicate upregulation, the blue box indicate downregulation, the black arrows indicate the directions of ion transport, and the yellow arrows indicate promotion.)

Table 1 Summaries of various ion channels and transporters antagonists experiment in the triple-negative breast cancer

| Ion channels and transporters | Transported ions | Alteration in TNBC | Roles in TNBC | Targeted TNBC cell lines | Antagonists |
|------------------------------|------------------|--------------------|---------------|--------------------------|-------------|
| AQP1                         | Water            | Upregulation       | Promote proliferation, migration, invasion and induce angiogenesis | CK14 (+) BLBC, 4T1 and MDA-MB-231 | Bacopaside I and bacopside II [32], Ginsenoside Rg3 [33] |
| AQP3                         | Water and small solutes | Upregulation       | Promote proliferation, migration and increase sensitivity to 5-fluorouracil chemotherapy | MDA-MB-231 | CuSO₄ [35] |
| Calcium modulator 1          | Ca²⁺             | Upregulation       | Promote proliferation, migration, invasion and angiogenesis | MDA-MB-231 | Phemindole [78] |
| NHE1 (SLC9A1)                | Na⁺ and H⁺       | Upregulation       | Promote proliferation, migration and growth, reduce sensitivity to paclitaxel | MDA-MB-231, MDA-MB-468 and Hs578T | Amiloride and cariporide [116], KR-33,028 [118] |
Abbreviations
AQPs: Aquaporins; BLBC: Basal-like breast cancer; BC: Breast cancer; CTRF: Cystic fibrosis transmembrane conductance regulator; CIC: Chloride channel; ENO-1: Enolase-1; ER: Estrogen receptor; EMT: Epithelial-mesenchymal transition; FGF-2: Fibroblast growth factor-2; FGFRK: FGFR: receptor kinase; HER-2: Human epidermal growth factor receptor 2; HERG1: Human Ether-a-go-go-related gene 1; HIF: Hypoxia-inducible factor; IGF1R: Insulin-like growth factor receptor; K2P (KCNK): Two-pore-domain potassium channels; MCU: Mitochondrial calcium unipporter; MMTV-PyVT: Mouse mammary tumor virus-driven polyoma virus middle T oncogene; NFAT: Nuclear factor of activated T-cells; NHE: Na+/H+ exchanger; Orai1: Calcium release-activated calcium modulator 1; PR: Progesterone receptor; ROS: Reactive oxygen species; SLC: Solute carrier; SOCE: Store-operated calcium entry; SOCCs: Store-operated calcium channels; STIM: Stromal interaction molecule; TNBC: Triple-negative breast cancer; TRPC: Canonical transient receptor potential.

Acknowledgements
We thank Guorong Wen, Hai Jin and Jiaxing An, who provided us with suggestions for the paper and support for daily experiments.

Authors’ contributions
CL and ZM made substantial contributions to the conception and design of the manuscript; XQ, HW, BT, XL and TL were involved in revising the manuscript critically for important intellectual content; all authors gave final approval of the version to be published. All authors read and approved the final manuscript.

Funding
This research was supported by the National Natural Science Foundation of China (81860098 to Taolang Li, 81860103 and 81560456 to Xuemei Liu and 81572438 to Biguang Tuo), the Joint Funds of the Science and Technology Foundation of Guizhou Province (J[2013]3) to Huihao Wu, the 15851 Talent Projects of Zunyi City to Taolang Li, and the Outstanding Scientific Youth Fund of Guizhou Province (2017-5608) to Xuemei Liu.

Availability of data and materials
Not applicable.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1 Department of Thyroid and Breast Surgery, Affiliated Hospital of Zunyi Medical University, Zunyi 563003, Guizhou Province, China. 2 Department of Gastroenterology, Affiliated Hospital of Zunyi Medical University, Zunyi, 563003, Guizhou Province, China. 3 Digestive Disease Institute of Guizhou Province, Zunyi, Guizhou Province, China.

Received: 19 April 2020 Revised: 26 July 2020 Accepted: 29 July 2020 Published online: 06 August 2020

References
1. DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, Jemal A, Siegel RL. Breast cancer statistics, 2019. CA Cancer J Clin. 2019;69(6):438–51.
2. Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F, Abdel-Rahman O, Abdelalim A, Abdoli A, Abdollahpour I, Abdulle ASM, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: a systematic analysis for the global burden of disease study. JAMA Oncol. 2019;5(12):1749–68.
3. Jafari SH, Saadatpour Z, Salamaninejad A, Momeni F, Mokhtari M, Nahand JS, Rahmati M, Mirzaei H, Kammehr M. Breast cancer diagnosis: imaging techniques and biochemical markers. J Cell Physiol. 2018;233(7):5200–13.
4. Dai X, Li T, Bai Z, Yang Y, Liu X, Zhan J, Shi B. Breast cancer intrinsic subtype classification, clinical use and future trends. Am J Cancer Res. 2015;5(10):2029–43.
5. Sarlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, Hastie T, Eisen MB, van de Rijn M, Jeffrey S, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA. 2001;98(19):10689–74.
6. Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y, Pietenpol JA. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest. 2011;121(7):2750–67.
7. Burstein MD, Timelzon A, Poage GM, Covington KR, Contreras A, Fuqua SA, Savage MJ, Osborne CK, Hillsenbeck SG, Chang JC, et al. Comprehensive genomic analysis identifies novel subtypes and targets of triple-negative breast cancer. Clin Cancer Res. 2015;21(7):1688–98.
8. Jhan JR, Andreckhe ER. Triple-negative breast cancer and the potential for targeted therapy. Pharmacogenom W. 2017;18(7):1595–609.
9. Ciriello G, Gatza ML, Beck AH, Wilkerson MD, Rhee SK, Pastore A, Zhang H, McElellan M, Yau C, Kandoth C, et al. Comprehensive molecular portraits of invasive lobular breast cancer. Cell. 2015;163(2):506–19.
10. Ma Z, Yuan D, Cheng X, Tuo B, Liu X, Li T. Function of ion transporters in maintaining acid-base homeostasis of the mammary gland and the pathophysiological role in breast cancer. Am J Physiol Regul Integr Comp Physiol. 2020;318(1):R98–r111.
11. Lin Y, Chang G, Wang J, Jin W, Wang L, Li H, Ma L, Li Q, Pang T. NHE1 mediates MDA-MB-231 cells invasion through the regulation of MT1-MMP. Exp Cell Res. 2011;317(14):2031–40.
12. Wang J, Xu H, Wang Q, Zhang H, Lin Y, Zhang H, Li Q, Pang T. CIAPIN1 targets Na+/H+ exchanger 1 to mediate MDA-MB-231 cells metastasis through regulation of MMPs via ERK1/2 signaling pathway. Exp Cell Res. 2015;333(1):60–72.
13. Yu C, Wang Y, Peng J, Shen Q, Chen M, Tang W, Lu X, Cai C, Wang B, Cai S, et al. Mitochondrial calcium unipporter as a target of microRNA-340 and promoter of metastasis via enhancing the Warburg effect. Oncotarget. 2017;8(48):83831–44.
14. Alvarez-Baron CP, Jonsson P, Thomas C, Dryer SE, Williams C. The two-pore domain potassium channel KCNK5 is induced by estrogen receptor alpha and role in proliferation of breast cancer cells. Mol Endocrinol. 2011;25(8):1526–36.
15. Wang L, Zhang Y, Wu X, Yu G. Aquaporins: new targets for cancer therapy. Technol Cancer Res Treat. 2016;15(6):821–8.
16. Nagaraju GP, Basha R, Rajitha B, Alese OB, Alam A, Pattnaik S, El-Rayes B. Aquaporins: their role in gastrointestinal malignancies. Cancer Lett. 2016;373(1):12–8.
17. Madeira A, Moura TF, Soveral G. Detecting aquaporin function and regulation. Front Chem. 2016;4:3.
18. Alistar A, Chou JW, Nagalla S, Black MA, D’Agostino R Jr, Miller LD. Dual roles for immune metagenes in breast cancer prognosis and therapy prediction. Genome Med. 2014;6(10):80.
19. Mobasher A, Barrett-Jolley R. Aquaporin water channels in the mammary gland: from physiology to pathophysiology and neoplasia. J Mammary Gland Biol Neoplasia. 2014;19(1):91–102.
20. Grimm SL, Rosen JM. The role of C/EBPbeta in mammary gland development and breast cancer. J Mammary Gland Biol Neoplasia. 2003;8(2):191–204.
21. Papadopoulos MC, Saadoun S. Key roles of aquaporins in tumour biology. Biochim Biophys Acta. 2015;1848(10 Pt B):2576–83.
22. Dajani S, Sanpalli A, Sharma-Walia N. Water transport proteins-aquaporins (AQPs) in cancer biology. Oncotarget. 2018;9(91):36392–405.
23. Kasa P, Farran B, Prasad GLV, Nagaraju GP. Aquaporins in female specific cancers. Gene. 2019;700:60–4.
24. Tomita Y, Dorward H, Yool AJ, Smith E, Townsend AR, Price TJ, Hardingham JE. Role of aquaporin 1 signalling in cancer development and progression. Int J Mol Sci. 2017;18(2):290.
feature of a particularly aggressive subgroup of basal-like breast cancers. Breast Cancer Res Treat. 2010;120(1):67–76.
26. Shi Z, Zhang J, Luo L, Zhao H, Cheng J, Xiang J, Zhao C. Aquaporins in human breast cancer: identification and involvement in carcinogenesis of breast cancer. J Surg Oncol. 2012;106(3):267–72.
27. Hayashi Y, Edwards NA, Proescholdt MA, Oldfield EH, Merrill MJ. Regulation and function of aquaporin-1 in glioma cells. Neoplasia. 2009;11(9):777–87.
28. Eirew P, Stingl J, Raouf A, Turashvili G, Aparicio S, Emerman JT, Eaves CJ. A method for quantifying normal human mammary epithelial stem cells with in vitro regenerative ability. Nat Med. 2008;14(12):1384–9.
29. Hu J, Verkman AS. Increased migration and metastatic potential of tumor cells expressing aquaporin water channels. Faseb J. 2006;20(11):1892–4.
30. Esteva-Font C, Jin BJ, Verkman AS. Aquaporin-1 gene deletion reduces breast tumor growth and lung metastasis in tumor-producing MMTV-PyVT mice. Faseb J. 2014;28(3):1446–53.
31. Abreu-Rodríguez I, Sánchez Silva R, Martins AP, Soveral G, Toledo-Aral JJ, López-Barneo J, Echevarría M. Functional and transcriptional induction of aquaporin-1 gene by hypoxia; analysis of promoter and role of Hif-1a. PLoS ONE. 2011;6(12):e28835.
32. Palethorpe HM, Smith E, Tomita Y, Nakjhai V, Youl AJ, Price TJ, Young JP, Townsend AR, Hardingine JE. Bcapacisides I and II in act to inhibit the growth, migration and invasion of breast cancer cell lines. Molecules. 2019;24(19):5339.
33. Nakjhai V, Palethorpe HM, Tomita Y, Price TJ, Youl AJ, Pei JV, Townsend AR, Hardingine JE. Stereoselective anti-cancer activities of ginsenoside Rg3 on triple negative breast cancer cell models. Pharmaceutica (Basel). 2019;3:117.
34. Zhu Z, Jiao L, Li T, Wang H, Wei W, Qian H. Expression of AQP3 and AQP5 in breast cancer: functional and prognostic significance. J Breast Cancer. 2010;4(4):603–9.
35. Nakhjavani M, Palethorpe HM, Tomita Y, Smith E, Price TJ, Yool AJ, Pei JV, Zhu Z, Jiao L, Li T, Wang H, Wei W, Qian H. Expression of AQP3 and AQP5 in breast cancer: identification and involvement in carcinogenesis of breast cancer. J Surg Oncol. 2012;106(3):267–72.
36. Zeng J, Wang J, Li J, Xu W, Chen H, Guo Y, Li H, Zhang J, Zhang J, Zhang J. CFTR silencing inhibits the growth, migration and invasion of breast cancer cell lines. Biomed. 2019;4(2):72.
37. Zeng J, Wang J, Li J, Xu W, Chen H, Guo Y, Li H, Zhang J, Zhang J, Zhang J. CFTR silencing inhibits the growth, migration and invasion of breast cancer cell lines. Biomed. 2019;4(2):72.
38. Li LT, Jiang G, Chen Q, Zheng JN. Ki67 is a promising molecular target in breast cancer. J Surg Oncol. 2012;106(3):267–72.
39. Hug MJ, Tamada T, Bridges RJ. CFTR and bicarbonate secretion by [correction of bicarbonate secre] channel-3 inhibits breast cancer cell growth in vitro and in vivo. J Breast Cancer. 2018;23(2):1071–81.
40. Cross BM, Breitwieser GE, Reinhardt TA, Rao R. Cellular calcium dynamics in lactation and breast cancer: from physiology to pathology. Am J Physiol Cell Physiol. 2014;306(6):C515–26.
41. Cui C, Merritt R, Fu L, Pan Z. Targeting calcium signalling in cancer therapy. Acta Pharm Sin B. 2017;7(1):13–17.
42. Smiderle E, Uhlein P. Frequency decoding of calcium oscillations. Biochim Biophys Acta. 2014;1840(3):964–9.
43. Papp B, Boulard JP. Altered endoplasmic reticulum calcium pump expression during breast tumorigenesis. Breast Cancer. 2011;15:163–74.
44. Cross BM, Hack A, Reinhardt TA, Rao R. SPCA2 regulates Orai1 trafficking and store independent Ca2+ entry in a model of lactation. PLoS One. 2013;8(6):e67348.
45. March S, Pinton P. Alterations of calcium homeostasis in cancer cells. Curr Opin Pharmacol. 2016;29:1–6.
46. O’Grady S, Morgan MP. Calcium transport and signalling in breast cancer. Oncogene. 2013;32(18):2282–91, 91.e1-7.
Makena MR, Rao R. Subtype specific targeting of calcium signaling in breast cancer. Cell Calcium. 2020;85:102109.

Tian C, Zhu R, Zhu L, Qiu T, Cao Z, Kang T. Potassium channels: structures, diseases, and modulators. Chem Biol Drug Des. 2014;83(1):1–26.

McAndrew D, Grice DM, Peters AA, Davis FM, Stewart T, Rice M, Smart CE, Brown MA, Kenny PA, Roberts-Thomson SJ, et al. ORAI1-mediated calcium influx in lactation and in breast cancer. Mol Cancer Ther. 2011;10(3):48–60.

Yang Y, Jiang Z, Wang B, Chang L, Liu J, Zhang L, Gu L. Expression of STIM1 is associated with tumor aggressiveness and poor prognosis in breast cancer. Pathol Res Pract. 2017;213(9):1043–7.

Liu X, Wang T, Wang Y, Chen Z, Hua D, Yao X, Ma X, Zhang P. Orai1 is critical for Notch-driven aggressiveness under hypoxic conditions in triple-negative breast cancers. Biochim Biophys Acta Mol Basis Dis. 2018;1864(4):PA97–85.

Yang S, Zhang JI, Huang XY. Orai1 and STIM1 are critical for breast tumor cell migration and metastasis. Cancer Cell. 2009;15(2):124–34.

Cheng H, Wang S, Feng R. STIM1 plays an important role in TGF-β-induced suppression of breast cancer cell proliferation. Oncotarget. 2016;7(13):18686–78.

Chakraborty S, Ghosh S, Banerjee S, Santra A, Banerjee AK, Sen PC. Phemindole, a synthetic Di-indole derivative manages the store operated calcium entry (SOCE) to induce potent anti-carcinogenic activity in human triple negative breast cancer cells. Front Pharmacol. 2016;7:114.

Didiasova M, Zakrzewicz D, Magbolisen V, Nagaraj C, Balint L, Rohde M, Preisnitzer KT, Wygeocka M. STIM1/ORAI1-mediated CAC2 + influx regulates enolase-1 exteriorization. J Biol Chem. 2015;290(19):11983–99.

Wuytack F, Raeymaekers L, Missiaen L. PMR1/SPCA Ca2+ uniporter is critical for store-operated Ca2+ entry in human triple negative breast cancer cells. J Biol Chem. 2013;288(5):2747–92.

Iorio J, Meattini I, Bianchi S, Bernini M, Maranga V, Dominici L, Casella D, Vezzosi V, Orzalessi L, Nori J, et al. HERG1 channel expression associates with molecular subtypes and prognosis in breast cancer. Cancer Cell Int. 2018;18:93.

Crociota O, Gustoi L, Balzi M, Becchetti A, Wanke E, Olivettino M, Wymore RS, Arcangeli A. Cell cycle-dependent expression of HERG1 and HERG1B isoforms in tumor cells. J Biol Chem. 2003;278(5):4947–55.

Lansu K, Gentile S. Potassium channel activation inhibits proliferation of breast cancer cells by activating a senescence program. Cell Death Dis. 2013;4(6):e652.

Breuer EK, Fukushima-Lopes D, Dalheim A, Burnette M, Zartman J, Kaja S, Wells C, Campo L, Curtis KI, Romero-Moreno R, et al. Potassium channel activity controls breast cancer metastasis by affecting β-catenin signaling. Cell Death Dis. 2019;10(3):180.

Fukushima-Lopes DF, Hegel AD, Rau V, Wyatt D, Baker A, Breuer EK, Osipo C, Zartman JI, Burnette M, Kaja S, et al. Preclinical study of a Kv11.1 potassium channel activator as an antiangiogenic approach for breast cancer. Oncotarget. 2018;9(33):3321–37.

Dookeran KA, Zhang W, Stayer L, Argos M. Associations of two-pore domain potassium channels and triple negative breast cancer subtype in The Cancer Genome Atlas: systematic evaluation of gene expression and methylation. BMC Res Notes. 2017;10(1):475.

Linzell JL, Peaker M. The distribution and movements of carbon dioxide, bicarbonate and bicarbonate between blood and milk in the goat. J Physiol. 1975;244(3):771–82.

Andersen AP, Moreira JM, Pedersen SF. Interactions of ion transporters and ion channels with cancer cell metabolism and the tumour microenvironment. Philos Trans R Soc Lond B Biol Sci. 2013;368(1638):20130098.

Huang X, Jan LY. Targeting potassium channels in cancer. J Cell Biol. 2014;206(2):151–62.

comes N, Serrano-Albarrás A, Capiera J, Serrano-Novillo C, Condem O, Ramén YCS, Ferreteres J, Feliu A. Involvement of potassium channels in the progression of cancer to a more malignant phenotype. Biochim Biophys Acta. 2015;1848(10 Pt B):2477–92.

Olsen ML, Sontheimer H. Mislocalization of Kir channels in malignant glia. Glia. 2004;46(1):163–73.

Choi M, Scholl UI, Yue P, Bjorklund P, Zhao B, Nelson-Williams C, Ji W, Choy J, Patel A, Men C, et al. K+ channel mutations in adrenal aldosterone-producing adenomas and hereditary hypertension. Science. 2011;331(6018):378–72.

Urrego D, Tomczak AP, Zahed F, Stühmer W, Pardo LA. Potassium channels in cell cycle and cell proliferation. Philos Trans R Soc Lond B Biol Sci. 2014;369(1638):20130094.

Plummer HK, Yu Q, Cakir Y, Schuller HM. Expression of inwardly rectifying potassium channels (GIRKs) and beta-adrenergic regulation of breast cancer cell lines. BMC Cancer. 2004;4:93.

Breuer EK, Fukushiro-Lopes D, Dalheim A, Burnette M, Zartman J, Kaja S, Wells C, Campo L, Curtis KI, Romero-Moreno R, et al. Potassium channel activity controls breast cancer metastasis by affecting β-catenin signaling. Cell Death Dis. 2019;10(3):180.

Fukushima-Lopes DF, Hegel AD, Rau V, Wyatt D, Baker A, Breuer EK, Osipo C, Zartman JI, Burnette M, Kaja S, et al. Preclinical study of a Kv11.1 potassium channel activator as an antiangiogenic approach for breast cancer. Oncotarget. 2018;9(33):3321–37.

Dookeran KA, Zhang W, Stayer L, Argos M. Associations of two-pore domain potassium channels and triple negative breast cancer subtype in The Cancer Genome Atlas: systematic evaluation of gene expression and methylation. BMC Res Notes. 2017;10(1):475.

Linzell JL, Peaker M. The distribution and movements of carbon dioxide, bicarbonate and bicarbonate between blood and milk in the goat. J Physiol. 1975;244(3):771–82.

Pedersen SF, Stock C. Ion channels and transporters in cancer: pathophysiology, regulation, and clinical potential. Cancer Res. 2013;73(6):1658–61.

Andersen AP, Moreira JM, Pedersen SF. Interactions of ion transporters and ion channels with cancer cell metabolism and the tumour microenvironment. Philos Trans R Soc Lond B Biol Sci. 2014;369(1638):20130098.

Wakabayashi S, Hisamitsu T, Nakamura TY. Regulation of the cardiac Na+/H+ exchanger in health and disease. J Mol Cell Cardiol. 2013;61:68–76.

Alves C, Lee BL, Sykes BD, Fiegel L. Structural and functional analysis of the transmembrane segment parVII and parVIII of the NHE1 isoform of the Na+/H+ exchanger. Biochemistry. 2014;53(22):3658–70.

Lee SH, Kim T, Park ES, Yang S, Jeong D, Choi Y, Rho J. NHE1, an osteoclast-specific member of the Na+/H+ exchanger family, regulates osteoclast differentiation and survival [corrected]. Biochem Biophys Res Commun. 2008;369(2):320–6.

Jenkins EC Jr, Debnath S, Gundry S, Gundry S, Uyar U, Fata JE. Intracellular pH regulation by Na+/H+ exchanger-1 (NHE1) is required for growth factor-induced mammary branching morphogenesis. Dev Biol. 2012;365(1):71–81.

Martin C, Pedersen SF, Schwab A, Stock C. Intracellular pH gradients in migrating cells. Am J Physiol Cell Physiol. 2013;300(3):C490–S.

Rishkin SJ, Cardone RA, Harquindey S. Na+/H+ exchanger-1 (NHE1) is required for growth factor-induced mammary branching morphogenesis. Dev Biol. 2012;365(1):71–81.

Martin C, Pedersen SF, Schwab A, Stock C. Intracellular pH gradients in migrating cells. Am J Physiol Cell Physiol. 2013;300(3):C490–S.

Rishkin SJ, Cardone RA, Harquindey S. Na+/H+ exchanger-1 (NHE1) is required for growth factor-induced mammary branching morphogenesis. Dev Biol. 2012;365(1):71–81.
112. Amith SR, Wilkinson JM, Baksh S, Fliegel L. The Na+/H+ exchanger (NHE1) as a novel co-adjuvant target in paclitaxel therapy of triple-negative breast cancer cells. Oncotarget. 2015;6(2):1262–75.

113. Amith SR, Wilkinson JM, Fliegel L. Assessing Na(+)+/H(+) exchange and cell effector functionality in metastatic breast cancer. Biochim Open. 2016;2:16–23.

114. Andersen AP, Flinck M, Oernbo EK, Pedersen NB, Viuff BM, Pedersen SF. Roles of acid-extruding ion transporters in regulation of breast cancer cell growth in a 3-dimensional microenvironment. Mol Cancer. 2016;15(1):45.

115. Andersen AP, Samsøe-Petersen J, Oernbo EK, Boedtkjer E, Moreira JMA, Kvelborg M, Pedersen SF. The net acid extruders NHE1, NBCn1 and MCT4 promote mammary tumor growth through distinct but overlapping mechanisms. Int J Cancer. 2018;142(12):2529–42.

116. Mihaila RG. A minireview on NHE1 inhibitors. A rediscovered hope in oncohematology. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2015;159(4):519–26.

117. Harguindey S, Arranz JL, Polo Orozco JD, Rauch C, Fais S, Cardone RA, Reshkin SJ. Cariporide and other new and powerful NHE1 inhibitors as potentially selective anticancer drugs—an integral molecular/biochemical/metabolic/cellular approach after one hundred years of cancer research. J Transl Med. 2013;11:282.

118. Amith SR, Wilkinson JM, Fliegel L. KR-33028, a potent inhibitor of the Na(++)/H(+) exchanger NHE1, suppresses metastatic potential of triple-negative breast cancer cells. Biochem Pharmacol. 2016;118:31–9.

119. Parks SK, Pouyssegur J. The Na(+)/HCO3(-) Co-transporter SLC4A4 plays a role in growth and migration of colon and breast cancer cells. J Cell Physiol. 2015;230(8):1954–63.

Publisher’s Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.