



Potassium channels in breast cancer

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Abstract

Due to its high incidence breast cancer is still a major health problem worldwide since, although a high percentage of patients can be effectively cured there are still some concerns in patients' management. Several new biomarkers and potential targets for therapy have been identified but still the effects on patients' outcome is not fully satisfactory. In the last years it was shown that potassium channels belonging to the different subfamilies are overexpressed in primary breast cancers and several associations with clinic-pathological features and outcome have been investigated. In this context, altered ion channels expression may be useful for diagnostic and therapeutic purposes.

This short review focuses on the expression and clinical relevance of potassium channels in breast cancer, recapitulating past and recent findings in translational research.

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Introduction

Breast Cancer (BC) is often described as a single disease but it is well known that it is quite heterogeneous with differences in clinical features, prognosis and response to treatment [1]. The heterogeneity of BC is reflected in the differences in prognosis and treatment options, therefore several studies have been focused on defining the biological features of BCs to better stratify the patients into risk groups to be treated with different regimens. The currently used classification of BCs is based on the detection of four biomarkers: the estrogen and progesterone receptors (ER, PgR), the Human Epidermal Growth Factor Receptor 2 (HER2) and the proliferation index (evaluated through Ki67 staining). Based on such molecular classification, five main BC subtypes (Luminal A, Luminal B, HER2-positive, Triple-negative and Normal-like) with different prognosis can be

distinguished. To better manage BC patients, the identification of new diagnostic tools as well as novel targets for therapy is mandatory. Through these studies several potential biomarkers have been identified. According to the NCI Dictionary of Cancer Terms, a biomarker is defined as "a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease". Biomarkers can be used for diagnostic, prognostic and predictive purposes in oncology.

Data gathered so far suggest that several ion channels could serve as biomarkers since they are frequently overexpressed in BC and such expression associates with clinico-pathological features (Table 1).

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Ion Channels

It is now well known that ion channels are expressed in different human tumors modulating several cell processes. Thus, ion channels could be proposed as novel cancer biomarkers, after being validated in the clinical setting.

Ion channels are transmembrane proteins that regulate ion fluxes through a central pore. Ion channels are generally present on the cell membrane in three different conformations (Figure 1): the “open” conformation allows the ions flow through the channel, while when the channel is in the “closed” state the ion flux is avoided. The third conformational status is the “inactivated” one, in which the channel is open but unable of letting ions flow.

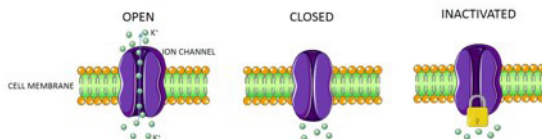


Figure 1: Schematic drawing of an ion channel in the “open” (left), “closed” (middle) and “inactivated” (right) conformational states.

The localization at the plasma membrane level suggests that ion channels might be good potential biomarkers since their detection might be easily performed for example by IHC and other molecular techniques; moreover they might also be blocked with specific drugs and antibodies. Several studies have been published in the last years to evaluate ion channels expression and potential use in BC management.

Among ion channels, potassium channels are key players that have been proven to be deregulated in several human cancers.

Potassium channels belong to a multi-gene family and several subfamilies have been identified (Figure 2): voltage-gated potassium channels, inward rectifiers, two-pore domains and calcium-activated channels (reviewed in [2]). Voltage-gated potassium channels are composed of four subunits surrounding an aqueous pore. Each subunit is made of six transmembrane domains (S1-S6): S4 is the voltage sensor while a loop between S5 and S6 defines the pore (P). Inward rectifiers are made of four subunits and each of them contains two transmembrane domain, linked by a P-loop. Two-pore domains channels are composed of four transmembrane domains and two regions that assemble to form the aqueous pore. Calcium-activated potassium channels represent a family with two groups of proteins: small- and intermediate- conductance (SK) and high-conductance potassium channels (BK). The SK channels are tetramers each composed by six transmembrane domains (S1-S6) with the central pore lying in the S5-S6 region; the BK channels are generally tetramers made of α (forming the pore) and β subunits.

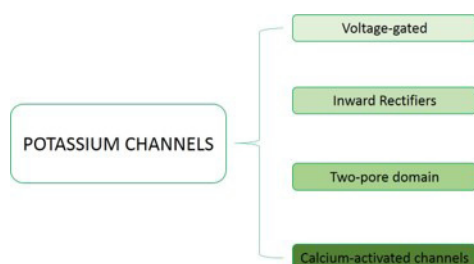


Figure 2: Potassium channels sub-families.

Potassium channels in breast cancer

From different studies performed over the last 20 years, several K⁺ channels have been proven to be overexpressed in primary BC and BC cell lines. A detailed list of potassium channels that have been proven to be expressed in BC (and their role, if known) is reported in (Table 1).

Long ago it was shown that a member of the voltage-gated family (Kv1.1, also known as KCNA1) is expressed in BC cell lines and it is involved in cell proliferation [3].

Kv1.3 channels, encoded by KCNA3 gene, are expressed in BC cell lines and are involved in apoptosis and proliferation [4]. Kv1.3 channels are also expressed in primary BC and their expression is associated with poor prognosis [4] and advanced stage [5].

Another member of the Voltage-gated subfamily, Kv4.1, is also expressed in BC cell lines and regulates cell proliferation [6].

Kv10.1 (also known as Eag1 or KCNH1) is a voltage-gated potassium channel that is expressed in human tumors while it is absent in the corresponding normal tissues [7] and long ago it was shown that in BC cell line MCF-7 Kv10.1 is one of the channels involved in proliferation and cell cycle progression [8] and migration [9]. Moreover, high Kv10.1 levels have been found in human BCs [10] both at the mRNA and protein levels by means of Real Time PCR and IHC, respectively. Different Authors showed that Kv10.1 is more expressed in invasive-ductal carcinomas than in fibro adenomas [11] and it was shown that calcitriol (that has anti-proliferative effects) reduces Kv10.1 expression by a mechanism based on vitamin D receptor. The same group also demonstrated that the combination of calcitriol and astemizole has a higher efficacy in reducing Kv10.1 expression [12]. More recently, it was shown that Kv10.1 is expressed at higher levels in TN BCs with respect to other molecular subtypes and that it correlates with tumor dimensions, stage and lymph node involvement [13].

Recently, it was shown that in BC cells SKBR3 and MDA-MB-231 the exposure to Kv11.1 channel agonist (NS1643) causes the cell cycle to stop in G0/G1 and induces cell senescence [14]. It was also demonstrated that Kv11.1 stimulates p21waf/cip transcription in BC cell lines [15]. The same group, analyzing public datasets, also showed that KCNH2 gene is overexpressed in BC [16]. To our knowledge, no data have been published regarding Kv11.1 protein expression in primary BC yet. We recently demonstrated that Kv11.1 protein is over-expressed in primary BC and found interesting correlations with clinico-pathological features and outcome [17]. These data might be of great clinical interest since Tamoxifen (used for BC treatment) was shown to block Kv11.1 currents [18], therefore it could be argued that Kv11.1 might serve as a therapeutic target and predictor of response to therapy.

Among the members of the Inward Rectifiers subfamily, it was demonstrated that Kir3.1 (also known as KCNJ3) channels are expressed in BC and positively correlate with the presence of lymph node metastases [19]. More recently it was also shown that Kir3.1 is associated with ER expression and represents an independent indicator of poor prognosis in ER⁺ tumors [20]. Other members of the Inward Rectifier subfamily are involved in cell cycle progression (Kir2.2, Kir6.1 and Kir6.2) [21,22], apoptosis and proliferation (Kir6.1 and Kir6.2) [22].

A member of the Two-pore subfamily (K_{2p} 5.1 also known as KCNK5 or TASK2) regulates BC proliferation [23] and its expression is induced by estrogens in ER+ BC cells, thus it was suggested as a potential therapeutic target for ER+ patients [23]. The KCNK9 gene encoding for K_{2p} 9.1 (also known as KCNK9 or TASK3), a member of, is amplified in BC and the corresponding protein is over-expressed. Such protein regulates cell migration in BC cell lines [24].

Three members of the Calcium-activated subfamily have been shown to be expressed in BC. KCa1.1 is expressed in BC cell lines and regulates apoptosis and migration [25]; in primary BCs, KCa1.1 expression correlates with ER [26], the occurrence of brain metastases [27], high stage, nuclear grade, proliferation and poor prognosis [28]. KCa2.3 regulates BC cell migration [29] while the expression of KCa3.1 (also known as KCNN4) has been demonstrated in BC cell lines, in which it is involved in migration and proliferation [30] while in primary BCs it correlates with high grade tumors with negative lymph nodes [31].

Finally, in a paper published in 2013 [32], a molecular signature of ion channels in BC was defined. Briefly, 280 ion channel genes were collected and eight independent microarray BC datasets from different countries (Singapore, France, Germany, Netherlands, Sweden, Taiwan and the United States) were analyzed. 22 differentially expressed ion channel genes (5 up-regulated and 17 down-regulated) were identified in p53 mutant tumors with respect to wild type ones. The second point of this study was the identification of differentially expressed ion channel genes between ER+ and ER- BC patients. Through this analysis it was shown that 16 genes were up-regulated and 8 genes were down-regulated in ER+ patients. Of these 24 genes, 19 overlapped with the differentially expressed genes identified in the comparison between mutant and wild type p53 patients and, among these common genes, it emerged that all the down-regulated genes in ER+ patients were up-regulated in patients bearing p53 mutations. The third point of the study was to investigate the possible relationships between ion channel gene expression and histological tumor grade and a correlation was demonstrated for 30 ion channel genes. Based on these findings, the Authors defined these ion channel genes as the “IC30 gene signature” and it was proven to be a good and independent biomarker to predict clinical outcome in BC patients. More recently, an in silico analysis of public datasets was performed [16] and the high expression of KCNH2 was demonstrated. These data are quite interesting since they are in accordance with our recent findings concerning the expression and clinical relevance of Kv11.1 channels in BC primary samples [17].

Potassium channels as therapeutic targets in breast cancer

In the recent years several evidences have been gathered concerning the potential use of potassium channels (together with other ion channels) as therapeutic targets. In this field, two of the most studied potassium channels are represented by Kv10.1 and Kv11.1, as described above. It was shown in vivo, that using astemizole (a Kv10.1 blocker already used in the clinical setting) significantly reduced in vivo growth of MDA-MB435S xenografts [33]. More interestingly, it was shown that the combined treatment with astemizole and calcitriol resulted in sharp reduction of the tumor masses in T-47D xenografts as well as in mouse models obtained with primary BCs [12].

The importance and role of Kv11.1 in several human solid cancers has been clearly defined and described also as a potential target for therapy [34,35] and it was shown that the combination of specific blockers of the channels together with drugs already used in the clinical practice (such as Bevacizumab) almost completely inhibit tumor growth in in vivo models [35]. More recently, it was shown that metastasis of breast cancer cells in vivo was reduced when the Kv11.1/ β 1 integrin complex (present in cancer cells but not in the heart) was broken [36], thus opening the possibility of exploiting also the Kv11.1/ β 1 integrin complex as a target for therapy.

Conclusion

The possibility of including into routine clinical practice a panel of biomarkers that might give more information useful for the management of BC patients is quite intriguing, although further validation studies are warranted. Among the genes included in the “IC30 gene signature” there are some potassium channels already described as being involved in BC: in particular, *KCNMA1* and *KCNN4* genes have been found to be associated to more aggressive tumors (metastasizing to lymph nodes and brain, high grade and poor prognosis). This is of particular relevance since they are both Calcium-activated potassium channels and their deregulation in BC could be thus linked to calcium homeostasis.

Tables

Table 1: Potassium channels sub-families.

Family	HGNC name	IUPHAR name	Alternative names	Gene	Chromosome location	Cell lines	Cinical correlations
Voltage-gated	KCNA1	Kv1.1	RBK1, HUK1, MBK1, AEMK	KCNA1	12p13.32	Proliferation [1]	
	KCNA3	Kv1.3	MK3, HLK3, HPCN3	KCNA3	1p13.3	Apoptosis, proliferation [2]	Poor prognosis, advanced stage [2,3]
	KCND1	Kv4.1	-	KCND1	Xp11.23	Proliferation [4]	
	KCNH1	Kv10.1	eag1	hEAG1	1q32.2	Proliferation [5], cell cycle progression [6], migration [7]	Overexpression [8], correlation with vit D receptor in invasive ductal carcinomas [9], poor prognosis [10], high expression in TNBC, association with stage, positive lymph nodes, higher expression in invasive ductal carcinomas [11]
	KCNH2	Kv11.1	hERG1	hERG1	7q36.1	Cell senescence [12], p21waf/cip transcription [13]	KCNH2 gene overexpression [14], correlation with molecular subtype, grading, ER, ki67 [15]
Inward Rectifier	KCNJ3	Kir3.1	GIRK1, KGA	KCNJ3	2q24.1	Apical localization [17]	Lymph node metastases [17], association with ER, independent prognostic factor (OS and DFS) [18]
	KCNJ8	Kir 6.1		KCNJ8	12p12.1	Apoptosis, cell cycle, proliferation [19]	-
	KCNJ11	Kir 6.2	BIR	KCNJ11	11p15.1	Apoptosis, cell cycle, proliferation [19]	-
	KCNJ12	Kir 2.2	Kir2.2v, IRK2, hIRK1	KCNJ12	17p11.2	Cell cycle [20]	-
Two-pore Domain	KCNK5	K2P5.1	TASK2	KCNK5	6p21	Induced by estrogens in ERa-positive cell lines], proliferation [21]	-
	KCNK9	K2P9.1	TASK3	KCNK9	8q24.3	Migration [22]	-
Calcium-activated	KCNMA1	KCa1.1	mSLO1	KC-NMA1	10q22	Migration [23], Apoptosis [24],	High stage, high grade, proliferation, poor prognosis [25], brain metastases [26]
	KCNN3	KCa2.3	hSK3, SKCA3		1q21.3	Migration [27]	-
	KCNN4	KCa3.1	hSK4, hKCa4, hKCa1	KCNN4	19q13.2	Proliferation [28]	High grade with negative lymph nodes [29]

TNBC: Triple-Negative BC; ER: Estrogen Receptors; OS: Overall Survival; DFS: Disease-Free Survival

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