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Review

KCa and Ca^{2+} channels: The complex thought ☆

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ABSTRACT

Potassium channels belong to the largest and the most diverse super-families of ion channels. Among them, Ca^{2+}-activated K^+ channels (KCa) comprise many members. Based on their single channel conductance they are divided into three subfamilies: big conductance (BKCa), intermediate conductance (IKCa) and small conductance (SKCa; SK1, SK2 and SK3). Ca^{2+} channels are divided into two main families, voltage gated/voltage dependent Ca^{2+} channels and non-voltage gated/voltage independent Ca^{2+} channels. Based on their electrophysiological and pharmacological properties and on the tissue where there are expressed, voltage gated Ca^{2+} channels (Cav) are divided into 5 families: T-type, L-type, N-type, P/Q-type and R-type Ca^{2+}. Non-voltage gated Ca^{2+} channels comprise the TRP (TRPC, TRPV, TRPM, TRPA, TRPP, TRPML and TRPN) and Orai (Orai1 to Orai3) families and their partners STIM (STIM1 to STIM2). A depolarization is needed to activate voltage-gated Ca^{2+} channels while non-voltage gated Ca^{2+} channels are activated by Ca^{2+} depletion of the endoplasmic reticulum stores (SOCs) or by receptors (ROCs). These two Ca^{2+} channel families also control constitutive Ca^{2+} entries. For reducing the energy consumption and for the fine regulation of Ca^{2+}, KCa and Ca^{2+} channels appear associated as complexes in excitable and non-excitable cells. Interestingly, there is now evidence that KCa–Ca^{2+} channel complexes are also found in cancer cells and contribute to cancer-associated functions such as cell proliferation, cell migration and the capacity to develop metastases. This article is part of a Special Issue entitled: Calcium signaling in health and disease. Guest Editors: Geert Bultynck, Jacques Haiech, Claus W. Heizmann, Joachim Krebs, and Marc Moreau.

1. Introduction

K^+ channels are the most numerous and diverse ion channels in living organisms. These ion channels are widespread and regulate numerous functions. For example, they regulate cell excitability in nerve tissue by contributing to action potentials, whereas in "non-excitable" cells, they control K^+ homeostasis or cell volume. They also regulate molecular processes, such as hormone secretion. The large number of genes encoding K^+ channels reflects the multiple functions of these channels. Each type of channel has unique electrophysiological and pharmacological properties. Based on the amino-acid sequences of the various K^+ channel subunits, it is possible to classify them into four classes: inwardly rectifying K^+ channels (Kir channels); tandem pore domain K^+ channels (K2P channel); Ca^{2+}-activated channels (KCa channels: BKCa, IKCa and SKCa) and voltage-gated K^+ channels (Kv). BKCa channels are activated by changes in membrane potential (depolarization) and/or by increases in intracellular Ca^{2+} concentration. SKCa and IKCa are not voltage-dependent and are activated by low intracellular Ca^{2+} concentrations. Through its high Ca^{2+} sensitivity, SKCa plays a role in the regulation of signaling pathways involving Ca^{2+}, in both excitable and non-excitable cells. In excitable cells, such as neurons, they induce a repolarization or a hyperpolarization that closes voltage-gated Ca^{2+} channels or decreases the probability of their activation, thereby decreasing intracellular Ca^{2+} concentration. Their activation in non-excitable cells, such as epithelial/endothelial cells, increases Ca^{2+} entry through non-voltage gated Ca^{2+} channels, by increasing the Ca^{2+} driving force, leading to an increase in intracellular Ca^{2+} concentration.

Regulation of intracellular Ca^{2+} homeostasis involves both entry from extracellular space and Ca^{2+} from intracellular sources (endoplasmic reticulum; ER, mitochondria). The ubiquitous second messager Ca^{2+} is involved in many fundamental physiological functions, such as cell cycle control, survival, apoptosis, migration and gene expression. For each cellular function, specific spatial and temporal characteristics are required. Thus, altered Ca^{2+} signaling has been suggested as an important event in driving the expression of malignant phenotypes, such as proliferation, migration, invasion and metastases. Among Ca^{2+} entry pathways, two major classes of plasma calcium permeable channels mediate Ca^{2+} entry in response to various stimuli. Voltage-gated Ca^{2+} channels (Cav),

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which are activated by depolarizing membrane and the non-voltage gated calcium channel including transient receptor potential (TRP) family, Store Operated Channels (SOCs) and Store- independent Ca^{2+} channels (Arachidonate-regulated Ca^{2+} channel) that require two partners Orai (Ca^{2+} channel) and STIM (ER protein). Cav are mostly expressed in excitable cells whereas the non-voltage gated Ca^{2+} channels are the major Ca^{2+} entry pathways in non-excitable cells.

During the last decade, KCa channels were found to be expressed in various cancers. Moreover, among this KCa channel family, the SK3 channel SKCa has been described as selectively expressed in aggressive cancers and implicated in metastasis development by interacting with Orai1, a specific voltage independent Ca^{2+} channel. This complex is essential to activate Ca^{2+}-regulated stimulatory pathways for cell migration and bone metastases. Here we review the studies that present evidence of the complex's formation between KCa and Ca^{2+} channels and their potential involvement in cancer.

2. K_{Ca} and Ca^{2+} channels

2.1. K_{Ca} channels

2.1.1. Generalities

Potassium channels belong to the largest and the most diverse super-family of ion channels. Given the K^+ channel diversity, a K^+ Channel Nomenclature (*KCN*) was developed based on the name of the genes encoding for K^+ channel subunits (http://www.genenames.org/genefamilies/IC). The family of Ca^{2+}-activated K^+ channels (KCa) comprises many members that exhibit different single channel conductance and pharmacological profiles.

According to IUPHAR (International Union of Pharmacology; http://www.iuphar-db.org/DATABASE/ReceptorFamiliesForward?type=IC), KCa channels belong to 6TM/1P (6 transmenbrane segments/1 pore domain) family and can be divided into three subfamilies: big conductance (BKCa), intermediate conductance (IKCa) and small conductance (SKCa) (Fig. 1). SKCa, included SK1, SK2 and SK3 (*KCNN1*, *2*, *3*, KCa2.1, 2.2, 2.3 SK1, 2, 3), BKCa included KCa1.1 (*KCNMA1* ou Slo ou Slo1) and IKCa is also named KCa3.1 or SK4 or IK1 [1]. KCa channels are formed by a main α subunit and, for BKCa, by additional regulatory subunits. The α subunit contains 6 (IKCa and SKCa) or 7 (BKCa) TM. Four alpha subunits are necessary to form a functional KCa channel. The selectivity filter for K^+ ions and the pore of the channel are formed by the loop between the fifth and sixth TM domains. SKCa and IKCa channels are voltage-insensitive and activated by low concentrations of intracellular Ca^{2+}, in contrast to BKCa, which is activated by both voltage and intracellular Ca^{2+}. By hyperpolarizing plasma membranes KCa channels regulate neuronal and smooth muscle excitabilities. In neurons, they mediate the afterhyperpolarization (AHP) that follows a neuronal action potential (a more negative resting potential than the resting one). There are three AHP components (fast, medium and slow AHP) and while BKCa is believed to be responsible for the fast AHP [2], SKCa control medium AHP but not slow AHP [3].

2.1.2. BKCa channel

Since its discovery by Marty et al. in chromaffin cells [4], the α BKCa subunit has been found in the central nervous system and in peripheral tissues.

This channel is voltage and Ca^{2+} dependent. It activates for membrane potential higher than 20 mV and for intracellular Ca^{2+}

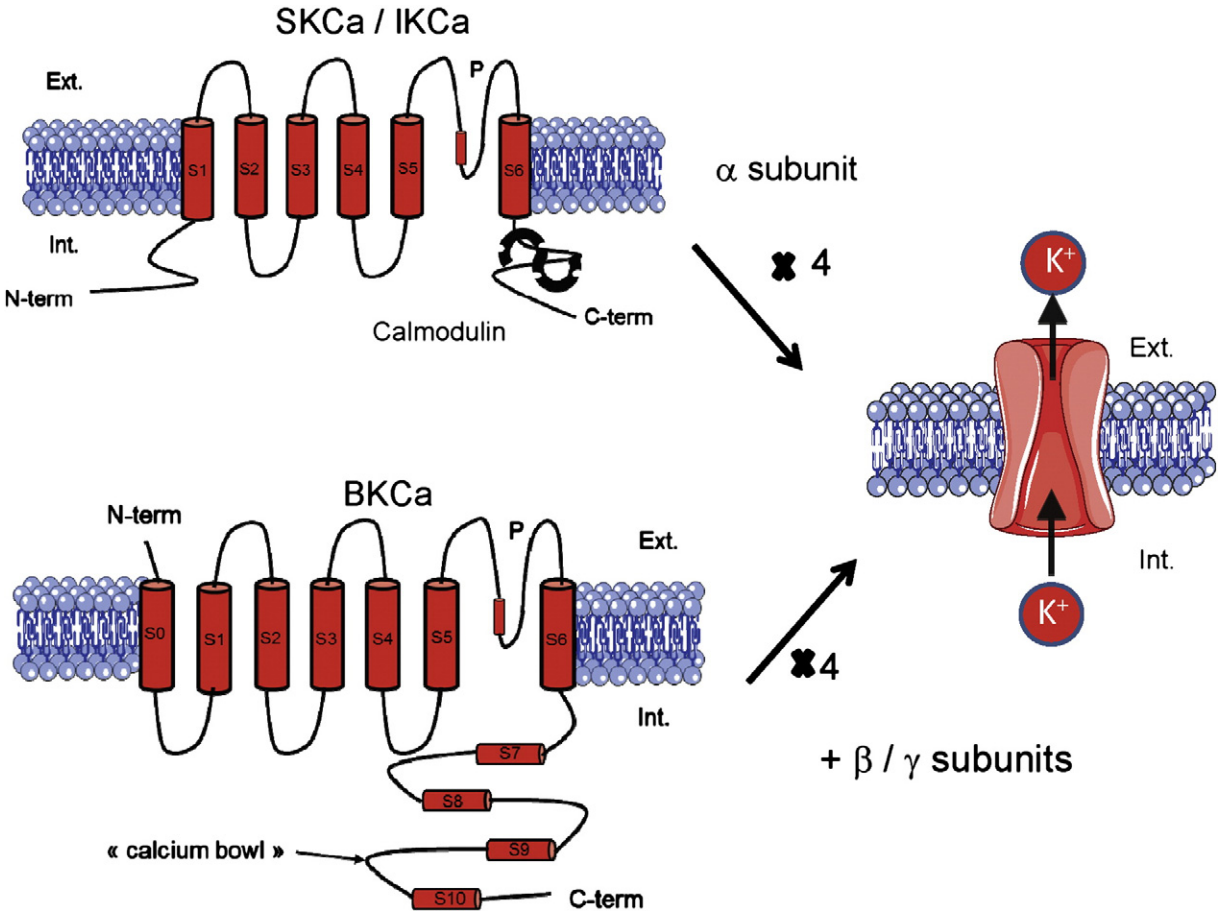

Fig. 1. KCa channels. Based on their single channel conductance, Ca^{2+}-activated potassium channels (KCa channels) are divided into three families that include large or big KCa (BKCa), intermediate KCa (IKCa/KCa3.1) and small conductance KCa (SKCa) channels. There are three isoforms of SKCa subunits, named SK1/KCa2.1, SK2/KCa2.2, SK3/KCa2.3. The α subunit associates to form tetramers, with β/γ subunits for BKCa or without known auxiliary subunit for SKCa/IKCa.

concentration above 300 nM. In smooth muscle cells this channel regulates the resting membrane potential through its activation by spontaneous Ca^{2+} release by the peripheral sarcoplasmic reticulum [5–7]. It plays a negative feedback controller role in excitation–contraction coupling by limiting smooth muscle cell depolarization and contractions [8]. In contrast to the voltage-independent SKCa and IKCa, which detect Ca^{2+} indirectly through association with calmodulin (CaM) [9,10], BKCa directly binds Ca^{2+} at its C-terminal region. There are three Ca^{2+} binding sites; two high affinity sites the "Ca^{2+} bowl" [11] and the RCK domain (Regulatory of Conductance of K^+) [12] and the low Ca^{2+} affinity binding site localized in the RCK domain.

Although BKCa activity is increased by membrane depolarization and by intracellular Ca^{2+} concentration, its activation is primarily induced by the voltage and not by Ca^{2+} [13–15]. Ca^{2+} acts as an amplifier, increasing channel activity at concentrations higher than 100 nM. Below this threshold, the channel works in a Ca^{2+}-independent mode and becomes purely voltage-dependent with a $V_{1/2}$ (voltage required for half-maximal Po (open probability)/activation) of 200 mV [13]. When the channel works in a Ca^{2+} dependent mode the $V_{1/2}$ linearly increase with pCa (free Ca^{2+}). The unique and singular properties of BKCa suggest that, in order to be active, it should colocalize with a Ca^{2+} channel or regulatory subunits that modulate its voltage and/or Ca^{2+} sensitivity.

The α subunit of the channel possesses a S0 segment which by its transmembrane position directs the N-terminal to extracellular side and allows the association with β subunits [16,17]. There are four β subunits (β 1–4 encoding by *KCNMB*) with 2 transmembrane segments connected with a large extracellular segment. These β subunits modulate its inactivation and deactivation kinetics as well as its inward rectification, Ca^{2+} sensitivity and toxin binding [13,15,18–24]. Globally, β subunits were found to differentially increase the Ca^{2+} sensitivity of BKCa. The effect of the β4 subunit on Ca^{2+} sensitivity was somewhat inconsistent in previous reports [21,25,26]. However, Ha et al. demonstrated that BKCa channel activation by Ca^{2+} became more cooperative by the coexpression of the β4 subunit [24]. Interestingly, the presence of β2 and β3 subunits resulted in rapid inactivation of BKCa currents, and β3 was found to induce inward rectification of the current–voltage relationship [19–23].

Additional group of auxiliary proteins to BKCa, the γ subunits, consists of proteins with a conserved leucine-rich repeat (LLCRs) that can dramatically modify BKCa channel activation [27,28]. Indeed, the LRRC26 induces a Ca^{2+}-independent leftward shift of ~140 mV in the opening probability *vs.* voltage curve. Other γ subunits are LRRC52 (γ2), LRRC55 (γ3) and LRRC38 (γ4) [28]. Interestingly, BKCa channels open at resting membrane potentials and low intracellular Ca^{2+} in the presence of γ subunits that are expressed in prostate cancer [28].

BKCa is blocked by several toxins such as Iberiotoxin, Paxilline and by low concentrations of extracellular Tetraethylammomium salt (TEA), and is activated by NS1608 and NS1619 [1]. Toxins are useful pharmacological tools to discriminate between KCa channels: BKCa is blocked by Iberiotoxin but not by Apamin, which specifically blocks SKCa channels. IKCa channels, which are not sensitive to Apamin and Iberiotoxin, are blocked by Charybdotoxin, this latter also inhibiting BKCa [29–32].

2.1.3. IKCa channel

Already in 1958 intracellular Ca^{2+} was shown to regulate K^+ efflux in red blood cells [33]. 26 years later patch clamp experiments revealed that the activation of a K^+ channel was responsible for this regulation [34]. The channel was cloned in 1997 [35–37] and is known under the names of IKCa, KCa3.1, SK4 or IK1. IKCa belongs to 6TM/1P channel family with a close SKCa structure.

Unlike for SKCa channels, the expression of IKCa transcripts was not found in excitable cells such as neurons and skeletal or heart muscles but mainly in the salivary glands, the placenta and the lungs [38]. On the other hand this channel was described to play an important role in lymphocytes activation [37,39]. Afterward, this channel was sporadically detected in some neurons where its role was not clearly established except for neurons from myenteric plexus where it was found to regulate the AHP [40,41].

Compared to SKCa channels IKCa have a larger conductance of about 40 pS at a symmetrical K^+ concentration (the identical concentration of K^+ in extra- and intracellular media) [35,36,38] and like for the SKCa current an inward rectification was described. The activation of this channel is not dependent on voltage but on intracellular Ca^{2+} concentration [35,36]. This is conferred by CaM binding in the C-term end of the channel, in a similar way as for SKCa [9]. Furthermore, the C-term region localized just after the pore of the channel is conserved with SKCa, and as demonstrated for SKCa, CaM can bind IKCa in the absence of Ca^{2+}. The origin of the intracellular Ca^{2+} elevation that activates IKCa depends on the cell type, but it is well accepted that in lymphocytes this is realized by Store Operated Ca^{2+} Entry activation [42,43].

Several papers have reviewed the pharmacological regulation of IKCa [44,45]. Briefly, IKCa is inhibited by various toxins, of which maurotoxin is the most selective one with an IC_{50} of about 1 nM [46]. Interestingly, maurotoxin produces no inhibition of SK1, SK2, SK3 and BKCa at up to 1 μM [46]. IKCa is also inhibited by Charybdotoxin, which, however, also acts on BKCa and Kv1.3 [29–32]. On the other hand, IKCa is also inhibited by various small molecules, the two being most used are Clotrimazole and TRAM-34. TRAM-34 is the most selective inhibitor of IKCa and was derived from Clotrimazole [47]. IKCa activators have also been synthesized, including benzimidazolone and benzothiazole compounds. These molecules are however not selective to IKCa, since they also activate SKCa channels.

2.1.4. SKCa channels

The genes coding for SKCa channels were cloned in 1996 [48]. Although they show no voltage sensitivity [48–50], the fourth transmembrane segment of the α subunit is positively charged, memory of the voltage-sensitive segment of Kv channels. The SKCa channels retain only two of the seven positively charged amino acids that are found in the S4 segment of Kv channels, and only one of these residues corresponds to the four arginine residues that carry the gating charges in Kv channels [48,51]. SKCa have been described in the central nervous system [50] but also in various cell types in the peripheral system, such as the skeletal muscle cells [52], the glandular cells [53] or the T lymphocytes [54].

There are three different genes encoding SKCa proteins, SK1, SK2, and SK3, which form channels with a conductance between 4 and 14 pS. They are mainly found in the central nervous system [55] as well in peripheral tissues, especially SK2 and SK3, while SK1 was detected almost exclusively in neuronal tissues [56].

Although the activation of SKCa channels is voltage independent, their current–voltage relationship shows an inward rectification that is the consequence of a voltage-dependent block by intracellular divalent cations [48,51]. Indeed, at positive membrane potentials, Ca^{2+} not only activates but also blocks SKCa channels in a concentration-dependent manner. Interestingly, this block is influenced by extracellular K^+, as observed for inward rectification K^+ channels family [57,58]. Low concentrations of intracellular Ca^{2+} (300–700 nM) activate SKCa channels to 50%, and the Hill coefficients of 3–5 that were deduced from Ca^{2+}-concentration response curves show a high degree of cooperativity for the Ca^{2+}-dependent activation of SKCa channels [10,51]. This suggests that the binding of more than one Ca^{2+} ion is necessary and that positive cooperative binding occurs [10].

The CaM binding site at the proximal portion of the C-terminus at each α subunit is highly conserved for the different SKCa subfamilies and is called CaM-binding domain (CaMBD) [59]. A SKCa channel has 4 CaMBD sites and 4 CaM would interact with CaM binding sites. The interaction between CaM and SKCa channel α subunits is constitutively maintained in the presence or absence of Ca^{2+}. SKCa channel activation requires each α subunit to be linked to CaM. CaM associated with each

α subunit must bind at least one Ca^{2+} ion for channel activation [7,60]. Ca^{2+} binding to CaM induces conformational rearrangements in CaM, which are transferred to the α-subunit, and results in SKCa channel opening. The N-terminal EF Hands of CaM (sites 1 and 2) are responsible for Ca^{2+}-dependent gating in SKCa channels whereas the C-terminal domain (sites 3 and 4) are necessary for Ca^{2+}-independent constitutive binding of CaM to SKCa [61].

The pharmacology of SKCa has already been discussed in excellent reviews [62–67]. Briefly, the modulation of SKCa channels by chemicals mainly occurs *via* three mechanisms: interaction with the pore of the channels (inhibitors or "pore blockers" such as Apamin), modification of the sensitivity of the channel to the cytosolic Ca^{2+} concentration (both inhibitors and activators) and amphiphilic structures acting by integration into the membrane (such as Ohmline).

2.2. Ca^{2+} channels

2.2.1. Non-voltage gated (voltage independent) Ca^{2+} channels

In 1883, Sydney Ringer was the first to highlight the important role of Ca^{2+} in cardiac contraction in the frog [68]. Since then numerous studies have shown the role of Ca^{2+} in many cellular processes such as muscle contraction, fertilization, secretion and differentiation. Changes in cytosolic Ca^{2+} trigger events critical for tumorigenesis, such as cellular migration, proliferation or apoptosis.

There are mainly two types of intracellular Ca^{2+} increase: following the release of intracellular stores (SOCE: Store Operated Ca^{2+} Entry), and the influx from the extracellular medium. The responsible ion channels for the former are the SOCS (Store Operated Channels), the CRAC (Ca^{2+}-Release Activated Ca^{2+} channel) being their archetype, and for the latter the chemo-dependent channels or SIC (Store Independent Ca^{2+} Channels). SIC include ROCs (Receptor Operated Channels), which are directly activated in response to extracellular signals to surface receptors without intracellular signalization, and SMOCs (Second Messenger Operated Channels), which are activated by an intracellular ligand (Diacyglycerol (DAG), phospholipase A2 (PLA2) or arachidonic acid (AA)) generated by the activation of G protein-coupled receptor.

The concept of SOCE was proposed in 1986 [69], but the molecular components of this pathway were not identified for almost two decades. Direct evidence in support of this model was provided by electrophysiological studies on Jurkat T cells and mast cells where the process of store depletion activated a Ca^{2+} current called Ca^{2+} release activated Ca^{2+} current or *I*CRAC [70,71]. *I*CRAC is non-voltage activated, inwardly rectifying, and highly selective for Ca^{2+} [72,73]. The single-channel conductance of *I*CRAC is ~15 fS [74] (total CRAC current from an entire cell is only ~5–10 pA) [75]. This slow, tiny but highly Ca^{2+}-selective CRAC current is the first and best characterized for SOCE.

The first candidate protein for a SOC was isolated from *Drosophila melanogaster* and called TRP (transient receptor potential) [76] which became the perfect prototype of channels activated by depletion of intracellular stores of Ca^{2+} [77,78]. Twenty-one genes code for proteins homologous to TRP and TRPL (TRP-Like) channels in *Drosophila*. TRP channels represent a new family which includes more than 50 cation-permeable channels. There are seven TRPC isoforms (TRPC1 to TRPC7), six TRPV (TRPV1 to TRPV6), and eight TRPM (TRPM1 to TRPM8) and TRPN, TRPA1, TRPP (TRPP1 to TRPP3) and TRPML (TRPML1 to TRPML3) [79]. On the structural level, the TRP super family adopts the same topology of 6 TM, similar to voltage gated K^+ channels. A small hydrophobic segment between the fifth and sixth TM domains participates in the formation of the pore channel. Like most channels with six TM domains, they are functional in homo- or heterotetramers. The S4 domain acts as a transmembrane electric sensor, giving a low voltage dependence for TRPs [80] (Fig. 2A). Whereas all TRP channels are permeable for various cations, only two are impermeable for Ca^{2+} (TRPM4, TRPM5), and two others are highly Ca^{2+} permeable (TRPV5, TRPV6).

At their N-termini, TRPC, TRPN and TRPV families have four ankyrin repetition domains, one of the most common protein–protein interaction motifs. Furthermore, TRPV6 and all TRPC contain interaction sites with CaM. The TRPC family constitutes a major subclass of the seven TRP subfamilies sofar identified to be regulated by store depletion [81–83]. Several studies on various cell lines have shown that TRPC4 and sometimes C5 can be activated by store depletion [84,85]. However, a new molecular identity to SOC channel may consist of a complex between STIM1 (Stromal Interacting Molecule 1) [86,87] and Orai1 [43,87] which were discovered as a result of a high-throughput screening by RNA interference (RNAi). In 2005, two groups independently screened Drosophila S2 and HeLa cells, and identified STIM as the molecule that senses ER Ca^{2+} levels and activates the opening of SOC channels on the plasma membrane [86,87]. In 2006, three other groups performed a pedigree analysis of inheritable severe combined immunodeficiency (SCID) patients whose lymphocytes lacked CRAC current. By genome-wide RNAi screening in Drosophila and human cells [43,88,89] Orai1 (or CRACM1 for CRAC modulator 1) was found to be another key molecule involved in SOCE. Subsequent studies have confirmed that Orai1 is the pore-forming protein of the SOC/CRAC channel [74,90,91]. Co-expression of STIM1 and Orai1 generates a huge CRAC like current [89,92,93], implying that the two molecules comprise the essential machinery for SOCEs [94–96].

STIM1 is the Ca^{2+} sensor of ER Ca^{2+} stores [86,97]. The *STIM1* is located on the human chromosome 11p15.5 [98]. A second gene, *STIM2* was identified with a structure very similar to *STIM1 and is located on the human chromosome 4p15.2*. Both proteins contain a single SAM domain and an EF-hand motif near the N-terminus, which is located in the ER lumen, which predicts a role of STIM1/2 in sensing ER Ca^{2+}. The cytosolic portion contains two coiled-coil domains, a Pro/Ser-rich and a Lys-rich stretch. The CRAC activation domain (CAD) is functionally recognized as the activation domains of Orai1 [99]. The protein STIM1 is expressed at both the cell surface and the ER, whereas STIM2 protein is expressed only in intracellular space [100]. STIM1 is known to have a dual role of ER Ca^{2+} sensor and transducer information to present to SOCs the plasma membrane. Depletion of intracellular Ca^{2+} stores causes rapid translocation and the formation of clusters of STIM1 is necessary for CRAC channel activation to the plasma membrane [101]. If STIM1 appears as a mediator of activation of SOCs, STIM2 is a potent inhibitor of this process, interfering with the action of STIM1 in preventing it from forming an aggregate. The opposite functions of STIM1 and STIM2 suggest that they may play a role in the control of Ca^{2+} entry *via* SOCs. STIM2 has been described as a feedback regulator that stabilizes basal concentrations of Ca^{2+} cytosol and ER. The suppression of STIM2 reduces cytosol and ER Ca^{2+} concentration whereas its overexpression leads to increase them [102].

Human Orai are plasma membrane proteins predicted to contain four TM segments (TM1 to TM4) with both N- and C-termini located in the cytosol. There are three isoforms of the Orai (Orai1, Orai2, Orai3) which are capable to form homo as heterotetramers [103] (Fig. 2B). In addition, the coexpression of STIM1, Orai2 and Orai3 also leads to the activation of a SOC but with different biophysical properties [103]. Orai1 includes a Proline-rich domain at its N-terminus and a coiled-coil domain at the C-terminus. The R91W mutation, located in TM1, was found in severe combined immunodeficiency (SCID) patients and abrogates Ca^{2+}-release-activated Ca^{2+} (CRAC) channel activity [43].

Concerning the role of TRP in SOCE, several studies have demonstrated a role of STIM1 in activating TRPC channels and regulating SOCE where STIM1 interacts with TRPC1 C2, C4 and C5 (for review [104]). Moreover, TRPC1 has been described to interact with Orai1 and STIM1 [105–108] and plasma membrane lipid rafts domains seem to determine the peripheral clustering of STIM1 and regulation of TRPC1-mediated SOCE [109–111]. However, the critical role of Orai1 in activation of TRPC1-SOC channels following Ca^{2+} store depletion has not yet been established but recent studies have showed a regulation of the surface expression of TRPC1 by Orai1 and gating by STIM1

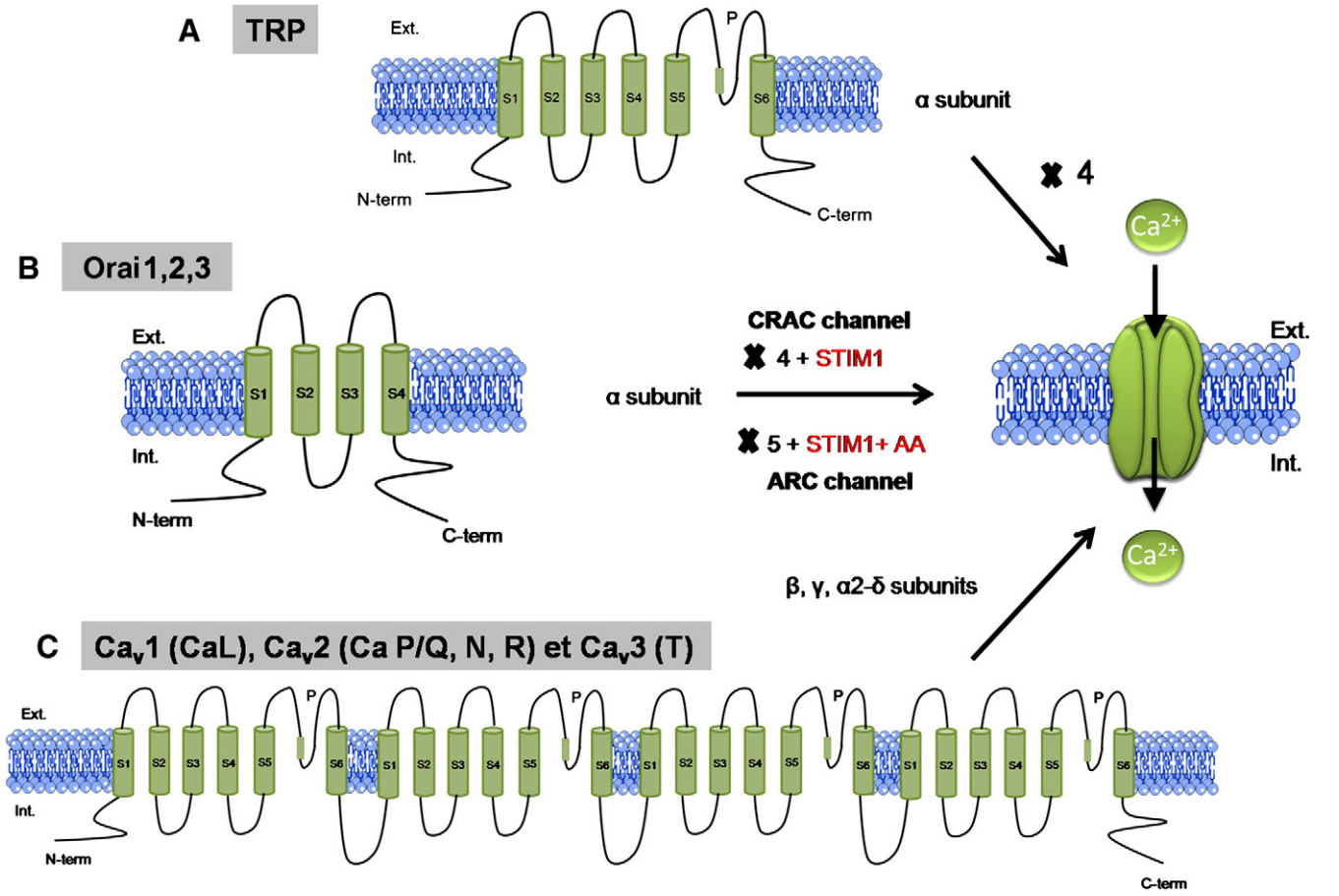

Fig. 2. Ca^{2+} channels are divided into non-voltage gated or voltage independent channels (TRP: transient receptor potential; Orai) and voltage gated or voltage dependent channels (Cav). A) TM topology of TRP. α subunit consisting of six TM domains with the N- and C-termini located in the cytoplasm. Between the fifth and sixth TM domains, which are highly conserved among all the homologues, there is a re-entrant pore loop (P). B) TM topology of Orai α subunit. Each has four TM spanning domains, with intracellular N and C termini. CRAC channel pore is formed from a tetramer of Orai1 subunits. ARC channel pore is formed from a pentameric assembly of Orai1 and Orai3 subunits. N-terminal cytosolic domain in Orai3 plays a critical role in sensitivity of the ARC channel to arachidonic acid. C) α subunit structure of Cav channels. Each subunit is organized in four homologous domains (I–IV), with six TM segments (S1–S6) each. The S4 segment is the voltage sensor and the pore loop is comprised between TM segments S5 and S6. An intracellular β subunit and $\alpha_2\delta$ subunit complex are components of most types of Ca^{2+} channels. A γ subunit has been found in skeletal muscle Ca^{2+} channels, and related subunits are expressed in heart and brain. Although these auxiliary subunits modulate the properties of the channel complex, the pharmacological and electrophysiological diversity of Ca^{2+} channels is linked to the multiple α_1 subunits.

following Ca^{2+} store depletion [112]. The TRP family, also called SMOCs, is activated by agonists acting on a range of G-protein-coupled receptors. There is a clear overlap between the functional roles played by SOCE and SMOC entry. There is a subtle distinction between one response, initiated by receptor activation but potentiated by the release of Ca^{2+} from intracellular stores and another initiated by store depletion as a consequence of receptor activation. Thus it is not surprising that, from a molecular point of view, both SOC and SMOC channels may be formed from proteins belonging to the same family. TRP channels initially were regarded as having a role in forming SOCs, however, many of their properties are consistent with them forming SMOCs. Thus, the association of TRPC5 with either TRPC1 [113] or TRPC4 [114] forms non-selective cation channels activated by G-protein coupled receptors, but not store depletion, as does expression of TRPC6 alone [115,116]. TRPC6, TRPC7 and TRPC3 have been reported to form channels activated directly by DAG [117,118]. TRPV4 contributed to an ATP-induced increase in mouse airway epithelial cells, providing a pathway for ROC entry but not SOCE [119]. Receptor-activated TRPC3, TRPC4 and TRPV4 may contribute to the regulation of Ca^{2+} entry and activity of endothelial vasodilator factors [120,121].

The Orai family includes store-independent Ca^{2+} channels or SMOC, arachidonic acid (AA)-regulated ARC channels [122,123]. The ARC channel is a small conductance, highly Ca^{2+}-selective ion channel whose activation is specifically dependent on low concentrations of arachidonic acid acting at an intracellular site [124]. The ARC channel pore is formed by a heteropentameric assembly of Orai1 and Orai3 subunits [125] (Fig. 2B). Like SOC channels, ARC channels depend on STIM1 for their activation, but whereas CRAC channel activation involves sensing the depletion of intracellular Ca^{2+} stores *via* a luminal N terminal EF-hand of STIM1 in the endoplasmic reticulum membrane, ARC channels are exclusively activated by the pool of STIM1 that constitutively resides in the plasma membrane [126,127]. In the same manner, activities of many TRP channels are regulated by lipids as PIP2 (phosphatidylinositol 4,5-bisphosphate), DAG or AA that can act as endogenous agonist. Thus, TRPV1, V3 and V4 can be activated by polyunsaturated fatty acids and AA metabolites [121,128–130]. Other studies have showed that TRPM8 is regulated by the Ca^{2+}-independent phospholipase A(2) (iPLA(2)) signaling pathway with its end products, lysophospholipids (LPLs), acting as its endogenous ligand [131,132].

2.2.2. Voltage gated (voltage dependent) Ca^{2+} channels

Among the major classes of plasma membrane Ca^{2+}-permeable channels, voltage-gated Ca^{2+} channels (Cav) have been the first described to control Ca^{2+} entry in excitable cells. They can also contribute to the regulation of Ca^{2+} entry in non-excitable cells (T-cells/cancer cells). However the mechanism by which Ca^{2+} enters electrically in non-excitable cells is unclear. Cav channels are heteromultimers that are composed of a pore-forming α1 subunit, β regulatory subunit, and α2, γ, and δ subunits [133]. The α1 pore subunit is predicted to have four repeated motifs (I–IV), each of which is hexahelical and contains

a loop between the S5 and S6 transmembrane segments that forms the channel pore (Fig. 2C). The S4 transmembrane segment in each motif contains conserved positively charged amino acids that are voltage sensors and that move outwards upon membrane depolarization, thereby opening the channel.

Since the first recordings of Ca^{2+} currents in cardiac myocytes [134], the classification of Ca^{2+} channel has been based on electrophysiological criteria associated with pharmacological criteria after the discovery of specific toxins [135–137].

According to these criteria, Ca^{2+} channels were divided into low-voltage activated (LVA) and high-voltage-activated (HVA). LVA Ca^{2+} channels activate at a membrane voltage positive to −60 mV. Because of the small amplitude of single channel conductance and its fast decay, these channels were also called T-type Ca^{2+} channels (T for tiny and transient). HVA channels have an activation threshold at membrane voltages positive to −40 mV. The first generally known representative of the HVA channel family was found abundant in skeletal, smooth and cardiac muscles as well as in neurons. Because of its large-single channel conductance amplitude and slow kinetics of current decay, it was named L-type Ca^{2+} channel (L for large and long-lasting) in contrast to the T-type. A pharmacological hallmark of all L-type channels is their sensitivity to 1,4-DHPs — a wide class of drugs with either inhibitory (Nifedipine, Nisoldipine, Isradipine).

Experiments with neuronal cells revealed novel Ca^{2+} channels, insensitive to DHPs and with single-channel conductance between those of T-type and L-type channels [138,139]. These channels were named N-type Ca^{2+} channels (N for neuronal). Neuronal non-L-type channels can be further classified into subtypes according to their sensitivity to peptide toxins isolated from cone snails and spiders. The channel sensitive to ω-Conotoxin kept the name N-type channel, while the channel sensitive to ω-Aga toxin was named P/Q-type channel [140]. The channels resistant to these toxins were named R-type Ca^{2+} channel (R for resistant).

The α1 subunit is responsible for basic electrophysiological and pharmacological properties that formed the basis of channel classifications. Several α1 subunits representing class L-type Ca^{2+} channels were identified. The first one, the α1 subunit from skeletal muscle was purified [141] and named α1S (*CACNA1S*) [142]. Later, α1 subunit was cloned from cardiac (*CACNA1C*) (α1C-a, [143]) and smooth muscle (α1C-b, [144]). L-type subfamilies were identified later: α1D (*CACNA1D*) ([145]; and α1F (*CACNA1F*) [146]). Three α1 subunits, representing the third neuronal types of Ca^{2+} channels, were cloned. α1A subunit (*CACNA1A*) [147,148] corresponds to the P/Q-type channel. α1B subunits (*CACNA1B*) [149] match with N-type channel. α1E subunit (*CACNA1E*) [150] was initially characterized as an LVA T-type channel. Later studies demonstrated that it has the properties of R-type channel. Three members of the LVA T-type subfamily were identified: α1G (*CACNA1G*) [151], α1H (*CACNA1H*) and α1I (*CACNA1I*). As the number of cloned Ca^{2+} channel α1 subunits increased a systemic nomenclature was defined: the Cavx.y scheme [152], where Cav stands for voltage-activated Ca^{2+} channel (VACC), x designating L-type, N-type and T-type, and y is a number designating individual members of subfamilies.

3. KCa–Ca^{2+} complexes

Despite the advancements over the past two decades in defining the expression and the role of channel proteins in cancer, many questions remain unanswered. For example, as channel proteins are hijacked from their normal physiological function: could KCa and Ca^{2+} channels form channel complexes in transformed cells, or in the context of tumors differ from those formed in a physiological context? Are these complexes linked to particular membrane structures (*e.g.*: some lipid rafts) specifically associated to malignant transformation or to the tumor microenvironment? Answering these questions should help to develop potent and specific inhibitors of these complexes in order to design therapeutic approaches specifically targeting tumor cells.

A depolarization is needed to activate voltage-gated Ca^{2+} channels while non-voltage gated Ca^{2+} channels are activated following Ca^{2+} ER depletion (SOCs), receptor activation (ROCs) or are constitutively active. A constitutive Ca^{2+} entry can also be observed for voltage-gated Ca^{2+} channels and for membrane potentials in which there is an overlap between the activation and inactivation curves, so that there is a window of membrane potentials over which a fraction of Ca^{2+} channels are activated but not inactivated. This is known as the Ca^{2+} window current. The increase of intracellular Ca^{2+} concentration through both voltage-gated and non-voltage gated Ca^{2+} channels activates KCa channels (Fig. 3ab). KCa activation by regulating the membrane potential would in turn alter the intracellular Ca^{2+} concentration depending on the voltage sensitivity of Ca^{2+} channels; the activation of KCa channels in excitable cells, such as neurons or smooth muscle cells, induces a repolarization or a hyperpolarization that closes voltage-gated Ca^{2+} channels, thereby decreasing intracellular Ca^{2+} influx through voltage gated Ca^{2+} channels (Fig. 3cd). In this case KCa channels play a crucial role in this negative feedback loop. In contrast, the activation of KCa channels in non-excitable cells, such as epithelial/endothelial cells, increases Ca^{2+} entry through non-voltage gated Ca^{2+} channels. This increases the Ca^{2+} driving force, leading to an increase in intracellular Ca^{2+} concentration (Fig. 3d). In this case KCa channels play a crucial role in this low-energy cost and positive feedback loop.

Table 1 reports publications that have established an association between KCa and Ca^{2+} channels in excitable and non-excitable cells. BKCa is the most frequent KCa channel associated with Ca^{2+} channels. Ca^{2+} channels provide sufficient Ca^{2+} for BKCa activity, acting as Ca^{2+} amplifiers. BKCa appears to be associated to voltage-gated and non-voltage gated Ca^{2+} channels in excitable and non-excitable cells, suggesting a role for this channel in either negative or positive feedback loops. SKCa and IKCa appear to be mostly expressed with voltage gated Ca^{2+} channels in excitable cells and with non-voltage gated Ca^{2+} channels in non-excitable cells respectively, suggesting a major role in the negative feedback loops for SKCa and positive feedback loops for IKCa. Interestingly, the SK3 channel switches from an association with voltage gated Ca^{2+} channels in excitable cells to non-voltage gated Ca^{2+} channels in cancer cells. This switch is believed to be used by cancer cells to increase Ca^{2+} entry subsequent to a positive feedback loop [153].

4. Role of KCa–Ca^{2+} channel complexes in the biology of cancer cells and tumor development

If in a physiological context, KCa and Ca^{2+} channels regulate neuronal and smooth muscle excitabilities, this is not that is observed in a tumor context. Their physiological function is hijacked by cancer cell to drive essential biological functions for tumor development such as cell migration [176–179]. KCa and Ca^{2+} channels have been found in many and various tumor cell lines, such as prostate cancer, breast cancer, gliomas, melanoma colon cancer and other tumors. These channels regulate functions such as cell proliferation and cell migration and this has been reviewed by several groups [67,177,178,180–186].

In this review we focused on recent findings demonstrating that KCa–Ca^{2+} channel complexes are also found in cancer cells that confer to these cells new biological functions such as cell proliferation and cell migration (Table 2).

Among them, we have demonstrated a pivotal role of SK3–Orai1 complex in cancer cell migration and bone metastasis development [153]. When SK3 channel is expressed in human breast and prostate epithelial cancer cells it co localize with Orai1 channel in lipid rafts (SK3 channel was not observed in normal human breast and prostate epithelial cells in contrast to Orai1 channel). The two channels form a complex acting independently of STIM1 and regulating a singular mode for Orai1-dependent Ca^{2+} entry. We propose to refer to this pathway as to a constitutive Ca^{2+} entry. We have been able to show that the disruption of SK3–Orai1 complexes by the alkyl-lipid Ohmline impaired the constitutive Ca^{2+} entry, cell migration and bone metastases. It is

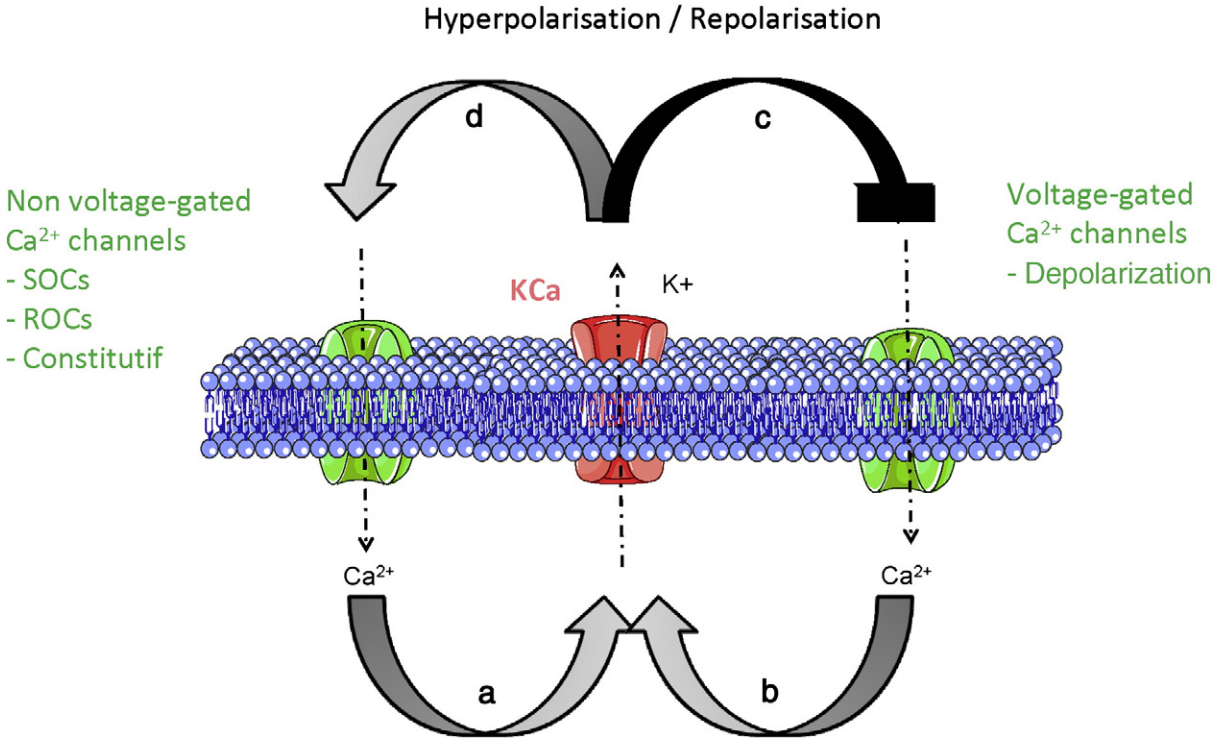

Fig. 3. Non-voltage gated (voltage insensitive) and voltage gated (voltage sensitive) Ca^{2+} channels working as ion channel complexes with KCa channels. SOCs; Store Operated Channels, ROCs; Receptor Operated Channels. a, d: positive feedback loop between KCa and Ca^{2+} channels, b, c: negative feedback loop between KCa and Ca^{2+} channels.

worth noting that primary human tumors and bone metastases from clinical samples were shown positive for a membrane-bound co-localized form of SK3 and Orai1. This strongly emphasizes the clinical consistency of our observations. We believe that formation of a SK3–Orai1 complex represents the gain of a new biological function, not existing either through individual protein or when the complex is not integrated into lipid rafts. This suggests that the evolving cancer cell could take advantage of the association and retargeting of two ion channels. SK3 and Orai1 are probably not the only actors of this constitutive Ca^{2+} entry. Indeed, a constitutive store independent Ca^{2+} entry that is

Table 1
Expression of KCa–Ca channel complexes in non-tumor cells. MVN; medial vestibular nucleus, DRG: Dorsal root ganglia, SMC: smooth muscle cells, HBE: human bronchial epithelial, M-1: cortical collecting duct, PBMC: peripheral blood mononuclear cells, coPI: CoImmunoprecipitation, IF: immunofluorescence, IH: immunohistochemistry, KCa: Ca^{2+}-activated K^+ channels, VGCa: voltage gated Ca^{2+} channels, N-VGCa: Non-voltage gated Ca^{2+} channel, and ND: not determined.

Cell type	KCa	VGCa	N-VGCa	Co-localization	Refs
Rat brain	BKCa	L-type Ca^{2+} channel		coIP and IH	[154]
Rat brain	BKCa	Cav1.2 / Cav2.1 / Cav2.2		coIP	[155]
Mesenteric artery SMC	BKCa	Cav1.2		IF	[156]
Hippocampal neurons	BKCa	N-type Ca^{2+} channel		ND	[157]
Neocortical neurons	BKCa	L/N-type Ca^{2+} channel		ND	[158]
Chromaffin cells	BKCa	L/Q-type Ca^{2+} channel		ND	[159]
tsA-201	BKCa	Cav3.2		coIP and IF	[160]
MVN					
Hair cells	BKCa	VGCa		IF	[161]
Hair cells	KCa	VGCa		IF	[162]
HEK293	BKCa		TRPV1	coIP and IF	[163]
DRG cells					
Cerebral SMC	BKCa		TRPV4/RyR	ND	[164]
HBE cell lines	BKCa		TRPV4	ND	[165]
Aorta SMC	BKCa		TRPC1	coIP and IF	[166]
HEK293	BKCa		TRPC3 / TRPC6	coIP and IF	[167]
Podocytes					
M-1 cell line	-BKCa		TRPV4	ND	[168]
HEK293	SK2 (alpha-actinin2)	Cav1.2 / Cav1.3		coIP and IF	[169]
Atrial and ventricular cardiac cells					
Hippocampal neurons	SKCa	L-type Ca^{2+} channel		ND	[157]
Dopaminergic midbrain neurons	SKCa	T-type Ca^{2+} channel		ND	[170]
Cerebral artery	-IKCa		TRPA1	IF	[171]
	-SK3				
PBMC Macrophages	IKCa		SOC	ND	[172]
HEK293					
MLS-9 microglia cells	IKCa		Orai1/SOC	IF	[173]
Human T lymphocytes	IKCa		TRPM7	ND	[174]
Endothelial cells	IKCa		TRPV4	Ca^{2+} imaging fluorescence	[175]

Table 2
Expression and biological functions of KCa–Ca channel complexes in tumor cells and tumor tissues. PCa: prostate cancer, LNM: metastatic lymph node samples, coPI: COlmmunoprecipitation, IF: immunofluorescence, IH: immunohistochemistry, KCa: Ca^{2+}-activated K^+ channels, VGCa: voltage gated Ca^{2+} channels, N-VGCa: Non-voltage gated Ca^{2+} channel.

Cell type	KCa	VGCa	N-VGCa	Co-localisation	Biological cell function	Refs
LNCaP PCa cell line	BKCa	Cav3.2		coIP and IF	Proliferation	[187]
LNCaP PCa cell line	IKCa		TRPV6	coIP	Proliferation	[188]
MDA-MB-435 s breast cancer cell line Breast and Prostate tumor tissues	SK3		Orai1	IF and IH	Migration	[153]
MDA-MB-231 breast cancer cell line Breast adenocarcinoma tissues and LNM	HEag1 (not a KCa)		Orai1	IH	Migration	[189]

formed by Orai1 and a secretory pathway Ca^{2+} ATPases 2 (SPCA2) has been described in breast cancer cells [190]. SPCA isoforms are important in sequestering Ca^{2+} and Mn^{2+} from the cytoplasm into the Golgi and post-Golgi vesicles. The two isoforms, SPCA1 (ATP2C1) and SPCA2 (ATP2C2) share significant sequence similarity, but have distinct distribution and function [191]. SPCA1 is ubiquitously expressed in mammalian tissues. In contrast, expression of SPCA2 is confined to highly secretory or absorptive epithelia, including the mammary gland, testis, salivary glands, intestinal tract, lung, and brain [192]. In breast cancer cells, Feng et al. showed that SPCA2 mRNA levels are upregulated and increased cell proliferation. The mechanism responsible revealed the ability of SPCA2 to be localized at the plasma membrane and to elicit a constitutive Ca^{2+} entry by an unconventional link between NH2-terminus SPCA2 and Orai1 [190]. The role of KCa channels in this complex is not known.

Interestingly, a recent paper describes a role for BKCa–Cav3.2 complex in the proliferation of LNCaP prostate cancer cells by controlling a constitutive Ca^{2+} entry [187]. BKCa–Cav3.2 complex, by maintaining membrane potentials within a window of membrane potentials over which a fraction of Cav3.2 are activated but not inactivated allows Ca^{2+} to constitutively enter the cells through this Ca^{2+} window current. This means that for these membrane potentials which are controlled by BKCa, Cav3.2 channels are open and support some entry of Ca^{2+} (we named constitutive Ca^{2+} entry). Furthermore, this constitutive Ca^{2+} entry would activate BKCa channels that regulate membrane potential working as a positive feedback loop (see Fig. 3). In this case Ca^{2+} acts as a modulator of BKCa activity thus controlling the membrane potential. Note that this Ca^{2+} window current did not activate IKCa channels (also expressed in these cells). A major difference between IKCa/SKCa and BKCa is the presence of regulatory subunits that could increase the Ca^{2+} sensitivity of BKCa channel. We can speculate that the Ca^{2+} window current is too small to reach the Ca^{2+} activation threshold of IKCa in contrast to BKCa. Since, it was found in LNCaP cells that the expression of γ subunits opens BKCa at resting membrane potentials and low intracellular Ca^{2+} [28,193], the necessary role of Cav3.2 for BKCa activity has to be determined.

IKCa was found to associate only with non-voltage gated Ca^{2+} channels both in tumor and non-tumor cells (see Tables 1 and 2). In LNCaP prostate cancer cells IKCa channel regulates Ca^{2+} entry through TRPV6 by controlling the electrochemical gradient for Ca^{2+} [188]. Moreover, immunoprecipitation experiments indicated a close physical interaction between the IKCa and TRPV6 in these cells [188]. In the same manner, the Human Ether a'-gogo potassium Channel 1 (hEag1) has been shown to regulate breast cancer cell migration through Orai1-dependent Ca^{2+} entry [189]. This complex has been found in invaded lymph nodes where high hEag1 level was associated with high Orai1 level expression [189]. However, in these two studies, the nature of Ca^{2+} entry (constitutive or capacitive) remains to be explored.

Similarly, the modification of expression or activity of other types of channel complex has been described to be involved in the disease process by decreasing the intracellular Ca^{2+} concentration. In glioma cell lines, TRPC1 channels, localize to the leading edge of migrating cells, where it has been correlated with EGF-mediated directional migration [194,195]. Interestingly TRPC1 that mediates Ca^{2+} entry seems to colocalize with the chloride channel ClC-3 in caveolar lipid rafts of glioma cells [196]. In fibrosarcoma cells, Cav3.1 channels have also been linked to metastatic behavior, probably in association with TRP channels [197].

5. Conclusion and future directions

In this review we focused on the KCa and Ca^{2+} ion channel families. Since Ca^{2+} activates KCa that pass through Ca^{2+} channels, their association as complexes seems to be an efficient and the economic way for their mutual fine regulation. There is now evidence that KCa and Ca^{2+} channels, alone or associated in complexes, play important roles in the proliferation and migration of cancer cells, crucial for metastatic development. Additional research is required to determine the role of these complexes in tumor development (primary tumor and/or metastatic development) and their clinical relevance. Many questions remain unanswered: Are KCa–Ca^{2+} channel complexes different in tumor cells compared to physiological context? Are these complexes linked to particular membrane structures (*e.g.* lipid rafts) associated with either malignant transformation or tumor microenvironment?

Answering these questions should help to develop potent and specific inhibitors of these complexes in order to design therapeutic approaches specifically targeting tumor cells. In this way we join our efforts and expertise within a French network named IonChannel-Canceropole Grand Ouest (IC-CGO; www.ic-cgo.fr). The IC-CGO project relies on a network composed of 19 partners from Grand Ouest region (including 2 platforms) with transversal, complementary and multidisciplinary approaches. The key objectives to be addressed by the IC-CGO network consist of complementary tasks: 1) to identify signaling complexes composed of KCa and Ca^{2+} channels involved in cancer cell migration and survival; 2) to determine the clinical relevance of these channels in breast cancer, prostate cancer, chronic lymphocytic leukemia and chronic myeloid leukemia; 3) to discover and develop new active modulators of these channels and complexes; 4) to develop appropriate cellular models for drug screening and ion channel probes for diagnostic and therapeutic approaches and 5) to test compounds on existing *in vitro* and *in vivo* platforms. We believe that this network will combine basic and clinical research through collaborations between clinicians, chemists and biologists, and allow us to propose KCa and Ca^{2+} channels as new relevant drug targets and prognostic indicators for breast cancer, prostate cancer and leukemia.

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