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Review

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

Maxime Guéguinou [a,b], Aurélie Chantôme [a,b], Gaëlle Fromont [a,b,c], Philippe Bougnoux [a,b,c], Christophe Vandier [a,b,*], Marie Potier-Cartereau [a,b]

[a] Inserm, UMR1069 "Nutrition, Croissance et Cancer", Tours F-37032, France
[b] Université François Rabelais, Tours 37032, France
[c] CHRU Tours, Tours, 37032 France

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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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* Corresponding author at: Inserm, UMR1069 "Nutrition, Croissance et Cancer", Tours F-37032, France. Tel.: +33 247366024; fax: +33 247366226.
*E-mail address:* christophe.vandier@univ-tours.fr (C. Vandier).

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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 $Ca^{2+}$

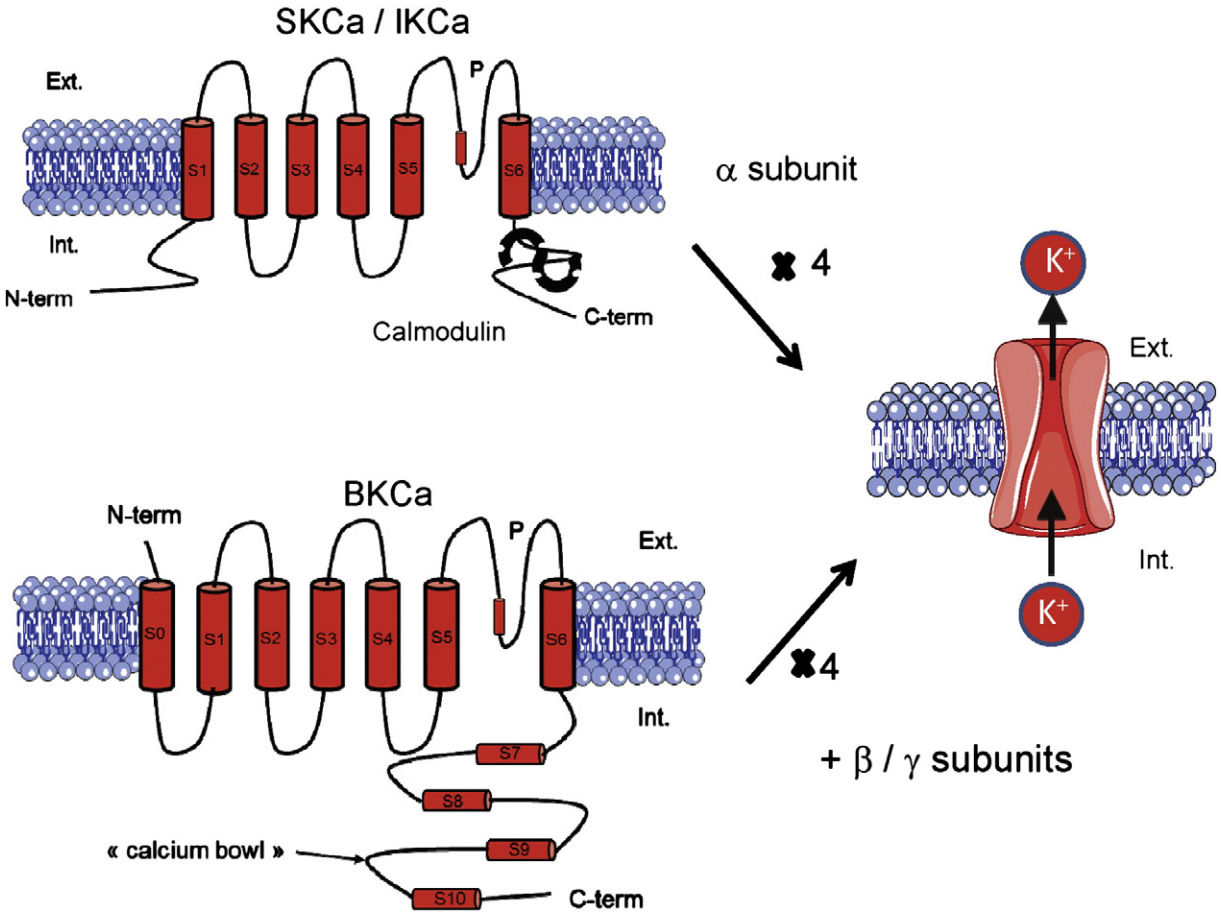


**Fig. 1.** KCa channels. Based on their single channel conductance, $Ca^{2+}$-activated potassium channels (KCa channels) are divided into three families that include large or big KCa (BKCa), intermediate KCa (IKCa/KCa3.1) and small conductance KCa (SKCa) channels. There are three isoforms of SKCa subunits, 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.