



Review

SK_{Ca}- and Kv1-type potassium channels and cancer: Promising therapeutic targets?

Maryne Dupuy^{a,*}, Maxime Gueguinou^b, Marie Potier-Cartereau^b, Frédéric Lézot^c,
Marion Papin^b, Aurélie Chantôme^b, Françoise Rédini^a, Christophe Vandier^b,
Franck Verrecchia^{a,*}

^a Nantes Université, Inserm UMR 1307, CNRS UMR 6075, Université d'Angers, CRCI2NA, F-44000 Nantes, France

^b N2C UMR 1069, University of Tours, INSERM, Tours, France

^c Sorbonne University, INSERM UMR933, Hôpital Trousseau (AP-HP), Paris F-75012, France

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ABSTRACT

Ion channels are transmembrane structures that allow the passage of ions across cell membranes such as the plasma membrane or the membranes of various organelles like the nucleus, endoplasmic reticulum, Golgi apparatus or mitochondria. Aberrant expression of various ion channels has been demonstrated in several tumor cells, leading to the promotion of key functions in tumor development, such as cell proliferation, resistance to apoptosis, angiogenesis, invasion and metastasis. The link between ion channels and these key biological functions that promote tumor development has led to the classification of cancers as oncochannelopathies. Among all ion channels, the most varied and numerous, forming the largest family, are the potassium channels, with over 70 genes encoding them in humans.

In this context, this review will provide a non-exhaustive overview of the role of plasma membrane potassium channels in cancer, describing 1) the nomenclature and structure of potassium channels, 2) the role of these channels in the control of biological functions that promotes tumor development such as proliferation, migration and cell death, and 3) the role of two particular classes of potassium channels, the SKCa- and Kv1- type potassium channels in cancer progression.

1. Introduction

Ion channels are transmembrane proteins that allow the passage of ions across membranes, such as the plasma membrane or the membranes of various organelles such as the nucleus, the endoplasmic reticulum, the Golgi apparatus or mitochondria [1]. These channels allow ions to diffuse according to their electrochemical gradient, schematically but depending of their charge and at physiological membrane potentials, from the most concentrated to the less concentrated compartment.

Some channels are mainly selective for a single type of ions, giving their names as sodium, calcium, chloride or potassium channels [2]. This selectivity is enabled by the presence of a selectivity filter, located at the channel pore, itself formed by the association of protein subunits [2]. However, some ion channels can allow the passage of more than one type of ions, such as TRPC (Transient Receptor Potential Cation) channels, which are permeable to both calcium and sodium [3]. Channel gating may depend on membrane potential (voltage-gated channels), ligand binding (ligand-gated channels), calcium or other stimuli such

Abbreviations: ARC, arachidonate-regulated Ca(2+)-selective channels; ATP, Adenosine Triphosphate; Bcl, B-cell lymphoma; BKCa, Big conductance calcium-activated potassium channel; Ca²⁺, Calcium; CaMBD, calmodulin-binding domain; CCE, Constitutive Calcium Entry; EAG K⁺ channel, ether-a-go-go potassium channel; ERK, Extracellular signal-regulated kinases; GPCR, G protein-coupled membrane receptor; HH, Hodgkin-Huxley; IC50, Half maximal inhibitory concentration; IKCa, Intermediate conductance calcium-activated potassium channel; IP3, Inositol tris-phosphate; K⁺, potassium; KCa, Calcium-activated potassium channel; Kir, inward-rectifier potassium channels; Kv, Voltage dependent potassium channel; NFAT, Nuclear Factor of activated T-cells; PKA, Protein Kinase A; PLC, phospholipase C; RTK, receptor tyrosine kinase; SICE, Store-Independent Calcium Entry; SKCa, Small conductance calcium-activated potassium channel; SMOC, Second Messenger Operated Channels; SOCE, Store-Operated Calcium Entry; SPCA2, Secretory Pathway Ca2+-ATPase; STIM, Stromal Interaction Molecule; TRP, Transient Receptor Potential; TWIK, tandem cancer cell.

* Corresponding authors.

E-mail addresses: maryne.dupuy@etu.univ-nantes.fr (M. Dupuy), franck.verrecchia@univ-nantes.fr (F. Verrecchia).

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stretch. Several mathematical models have been proposed to describe the opening and closing of ion channels. Mathematical modeling of channel opening and closing kinetics is generally based on a Hodgkin-Huxley (HH) or Hidden Markov Model (HMM) description [4–5]. The HH model offers a basic paradigm in which the channel can be opened or closed, enabling the activation, deactivation and inactivation phases of the channel. This HH model reproduces macroscopic currents fairly accurately. The HMM model specifies the channel states as a function of the protein conformation and takes into account the channel-specific gating behavior, thus enabling highly accurate and realistic modeling of channel kinetics. More recently Langthaler et al suggest a theoretic modeling approach combining the positive features and properties of the HH model and the HMM model [4].

The development of molecular biology has led to the consequent discovery of a number of genes coding for ion channel subunits, making the classification of ion channels less clear-cut. The latest classification by the British Pharmacological Society (BPS; <https://www.guidetopharmacology.org>) also takes into account, in a third category, ion channels which open in response to new stimuli: cell volume, temperature, the presence of an intracellular secondary messenger, such as calcium or ATP (Adenosine Triphosphate).

Ion channels were originally identified as being mainly found in the so-called excitable cells, such as neurons, muscle cells or cardiac cells [2] or so-called non-excitable cells such as epithelial cells [6]. The best-known function of ion channels is to control membrane potential. In excitable cells, ion channels enable the establishment of a resting membrane potential and the generation of an action potential [7]. In the so-called non-excitable cells, the passage of ions through the channel according to the electrochemical gradient has also a direct impact on both membrane potential and cell osmolarity [8–9]. Numerous studies have demonstrated the role of ion channels in cellular processes such as cell proliferation or cell cycle progression [10], cell migration [11–12], or apoptosis [13–14].

The term “channelopathy” was proposed in the 1990s to describe the link between hereditary disorders of human skeletal muscle contraction and mutations in the gene encoding the voltage-gated sodium channel in skeletal muscle [15]. A decade later, this term was used to designate any hereditary heart rhythm disorder, epilepsy or neuropathy resulting from mutations in this same gene [16]. Today, a channelopathy is broadly defined as a disease associated with ion channel dysfunction [17]. The term is no more limited to diseases linked to mutations in ion channel-encoding genes, but also encompasses pathologies associated with alterations in channel-encoding gene expression, aberrations in ion channel protein synthesis or their post-translational modifications [18].

As regards to cancer cells, they have acquired functional capacities, influenced by the cellular processes listed and defined for the first time by Hanahan and Weinberg under the term “cancer hallmarks” in 2000, then again in 2011 [19–20]: Self-sufficiency in growth signals, Insensitivity to anti-growth signals, Evading apoptosis, Limitless replicative potential, Sustained angiogenesis, Tissue invasion and metastasis, Avoiding immune destruction and Deregulating cellular energetics. Although not all cancer hallmarks are inherently linked to ion channel mutations, dysfunction, or abnormal expression, these may contribute to cancer progression. Indeed, as the function of some ion channels deregulates certain cellular processes, such as cell proliferation or migration, it is not surprising that they can play a crucial role in the development of cancers. This link between ion channels and cancer hallmarks therefore allows some cancers to be assigned to the category of onco-channelopathies. This process is defined as follows: a deregulation of the expression or activity of a channel impacts a cellular process involved in tumorigenesis, ultimately participating in the development of a cancer [21].

2. Potassium channels

Among ion channels, the most varied and numerous forming the

largest family, are the potassium channels, with over 70 genes encoding them in humans. Generally accepted, these channels are known to be responsible for nerve cell excitability, generating an action potential, but they may also be responsible for cell volume regulation or hormone secretion in electrically non-excitable cells [1]. Structurally, potassium channels can be recognized by a highly conserved amino acid sequence, commonly referred to as the “potassium channel signature sequence” [22]. This forms the selectivity filter, which enables potassium channels to have near-perfect selectivity to potassium ions.

These potassium channels are probably the channels that have the highest variability, both in terms of their biochemical structures and their roles in cancer. Abnormal expression of potassium channels in tumors has thus been documented for many tumor types [21,23–26]. This review thus focuses on the role of some of these channels, in particular SKCa- and Kv1- type potassium channels, two sub-families of K⁺ channels with 6 transmembrane segments and 1 pore domain, in cancer development.

2.1. Classification

On the basis of the structure and amino acid sequence homology between the different α -subunits forming the channel, this potassium channel superfamily has been divided into four subfamilies [27–29] (Fig. 1).

2.1.1. Potassium channels with 2 transmembrane segments and one pore domain

This category includes inward-rectifier potassium channels (K_{ir}) [30]. The N-terminal and C-terminal domains are cytosolic, and the pore domain is located between the two transmembrane segments. This family is divided into 4 groups:

- Classical K_{ir} channels: K_{ir}2.1, K_{ir}2.4, K_{ir}2.2 and K_{ir}2.3, whose α -subunits are encoded by the *KCNJ2*, *KCNJ14*, *KCNJ12* and *KCNJ4* genes, respectively,
- GIRK (G protein-coupled K_{ir} channels): K_{ir}3.1, K_{ir}3.3, K_{ir}3.4 and K_{ir}3.2, whose α -subunits are encoded by the *KCNJ3*, *KCNJ9*, *KCNJ5* and *KCNJ6* genes, respectively. Their opening is directly mediated by the binding of a G protein [31],
- K_{ATP} (ATP-sensitive K_{ir} channels): K_{ir}6.1 and K_{ir}6.2, whose α -subunits are encoded by the *KCNJ8* and *KCNJ11* genes. These channels are formed by the association of the subunits encoded by the above-mentioned genes with the SUR (sulfonylurea receptor) subunits. They are ATP-sensitive, which means that their opening depends on the binding of ATP to the Kir6 subunits and blocks the channel [32],

2.1.2. Potassium channels with 4 transmembrane segments and 2 pore domains

This subfamily includes the K2P potassium channels, also known as two-pore domain potassium channels [33]. Their N-terminal and C-terminal domains are cytosolic, and the two pore domains are located between transmembrane segments 1 and 2, and 3 and 4 respectively. Within this subfamily, channels are subdivided into 6 distinct groups [33]:

- TWIK (tandem pore domain weak inward rectifying potassium channel) comprises the *KCNK1*, *KCNK6* and *KCNK7* genes, encoding the α -subunits of the K_{2p}1.1, K_{2p}6.1 and K_{2p}7.1 channels, respectively. K_{2p}1.1 was the first gene encoding these subunits to be cloned in mammals [34],
- TREK (TWIK-related K⁺ channels) comprises the *KCNK2*, *KCNK4* and *KCNK10* genes, encoding the K_{2p}2.1 (TREK-1), K_{2p}4.1 (also named TRAAK for Twik-related arachidonic-acid stimulated K⁺ channel) and K_{2p}10.1 (TREK-2) α -subunits, respectively,

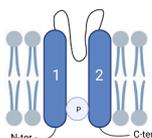
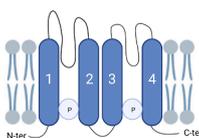
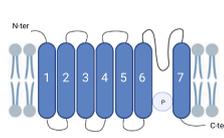
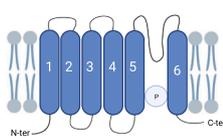
| | a | b | c | d |
|-----------------------------------|---|---|--|---|
| Transmembrane segments | 2 | 4 | 7 | 6 |
| Pore domain | 1 | 2 | 1 | 1 |
| Pore domain location | Between TS 1 and 2. | Between TS 1 and 2 and 3 and 4. | Between TS 6 and 7 | Between TS 5 and 6 |
| N-terminal and C-terminal domains | Cytosolic | Cytosolic | N-terminal: extracellular C-terminal: cytosolic | Cytosolic |
| Representation |  |  |  |  |
| Functional channel | Tetramer | Dimer | Tetramer | Tetramer |
| Examples | K _{ir} / GIRK / K _{ATP} | K _{2P} | BK _{Ca} | SK _{Ca} / IK _{Ca} / Kv |

Fig. 1. Potassium channels classification. Potassium channels are divided into 4 classes according to the amino acid sequence homology between the α subunit.

- TASK (TWIK-related acid-sensitive potassium channel) comprises the *KCNK3*, *KCNK5*, *KCNK9* and *KCNK15* genes, encoding the K_{2p}3.1, K_{2p}5.1, K_{2p}9.1 and K_{2p}15.1 channel α -subunits, respectively,
- THIK (Tandem pore-domain Halothane Inhibited K⁺ channel) comprises the *KCNK12* and *KCNK13* genes, encoding the α -subunits of the K_{2p}12.1 and K_{2p}13.1 channels, respectively,
- TALK (TWIK1-related alkalization-activated K⁺ channel) comprises the *KCNK16* and *KCNK17* genes, encoding the α -subunits of K_{2p}16.1 and K_{2p}17.1 channels, respectively,
- TRESK (TWIK-RELATED Spinal cord K⁺ channels) comprises the *KCNK18* gene, encoding the K_{2p}18.1 channel subunit. This is the latest gene identified for this family of potassium channels [35].

2.1.3. Potassium channels with 7 transmembrane segments and 1 pore domain

This third subfamily consists mainly of the big-conductance calcium-activated potassium channels (BK_{Ca} / KCa1.1 and KCa5.1) [36–37], whose first transmembrane segment is specific to these channels, while they share transmembrane segments S2 to S7 with voltage-gated potassium channels [38]. Unlike all the potassium channels mentioned above, their N-terminus is extracellular, while their pore domain is located between transmembrane segments 6 and 7 [39] and their activity is regulated by both membrane depolarization and intracellular

calcium concentration. The α -subunit of these channels is encoded by *KCNMA1* and *KCNU1* gene for KCa1.1 and KCa5.1 respectively. Interestingly, a membrane protein containing leucine-rich repeats (LRRs), LRR26, has been identified as an auxiliary subunit of the BK_{Ca} channels [40]. This protein identified in various tissues, causes a significant negative shift in the voltage dependence of channel activation leading to its activation at resting membrane potential of cancer cells [37]. We can note that there are large conductance sodium-activated potassium channels with 6 transmembrane segments instead of 7 [37].

2.1.4. Potassium channels with 6 transmembrane segments and 1 pore domain

Calcium-activated potassium channels (K_{Ca}) and voltage-gated potassium channels (Kv) constitute the fourth subfamily [38,41]. Like K_{ir} and BK_{Ca} channels, these channels are active as tetramers of α -subunits. Their N-terminal and C-terminal domains are cytosolic, and their pore domain is located between transmembrane segments 5 and 6.

Among K_{Ca} channels with 6 transmembrane segments and 1 pore domain two subfamilies are described:

- SK_{Ca} channels (Small-conductance K_{Ca} channels) comprise SK1 (KCa2.1), SK2 (KCa2.2) and SK3 (KCa2.3), whose α -subunits are encoded by the *KCNN1*, *KCNN2* and *KCNN3* genes, respectively,

- IK_{Ca} channels (Intermediate-conductance K_{Ca} channels) also named SK4 ($KCa3.1$), whose α subunit is encoded by the *KCNN4* gene.

Among the voltage-gated potassium channels (Kv), several sub-families ($Kv1-12$) exist, including the principal ones:

- Shaker-related: $Kv1.1$ to $Kv1.8$, whose α -subunits are encoded by the *KCNA1*, *KCNA2*, *KCNA3*, *KCNA4*, *KCNA5*, *KCNA6*, *KCNA7* and *KCNA10* genes, respectively,
- Shaw-related: $Kv3.1$ to $Kv3.4$, whose α -subunits are encoded by the *KCNC1*, *KCNC2*, *KCNC3* and *KCNC4* genes, respectively,
- Shab-related: $Kv2.1$ and $Kv2.2$, whose α -subunits are encoded by the *KCNB1* and *KCNB2* genes, respectively,
- Shal-related: $Kv4.1$ and $Kv4.2$, whose α -subunits are encoded by the *KCND1* and *KCND2* genes, respectively,
- M-channels: $Kv7.1$, $Kv7.2$, $Kv7.3$, $Kv7.4$ and $Kv7.5$ whose α -subunits are encoded by *KCNQ1*, *KCNQ2*, *KCNQ3*, *KCNQ4* and *KCNQ1*, respectively.
- EAG (ether-a-go-go potassium channels) divided into 3 categories. These include $Kv10.1$ and $Kv10.2$, the eag channels, whose α -subunits are respectively encoded by the *KCNH1* and *KCNH5* genes; erg

(eag-related gene) channels, with $Kv11.1$, $Kv11.2$ and $Kv11.3$ channels, whose α -subunits are encoded by the *KCNH2*, *KCNH6* and *KCNH7* genes; and elk (eag-like K^+ channels), with the $Kv12.1$, $Kv12.2$ and $Kv12.3$ channels, whose α -subunits are encoded by the *KCNH8*, *KCNH3* and *KCNH4* genes.

2.2. Potassium channels and key function in cancer progression

Like most ion channels, potassium channels are known to be involved in various key cellular processes in tumor development, such as cell proliferation, cell migration, cell invasion and cell death by apoptosis, and have been proven to be potential targets for cancer therapies (For recent reviews see [25,42–49]).

2.2.1. Cell proliferation

The mechanisms by which potassium channels regulate cell proliferation are the subject of several hypotheses, of which 4 are the most widely accepted [24,44].

2.2.1.1. Regulation of membrane potential. It was suggested that cancer cells, known to have a high proliferative state, have more depolarized

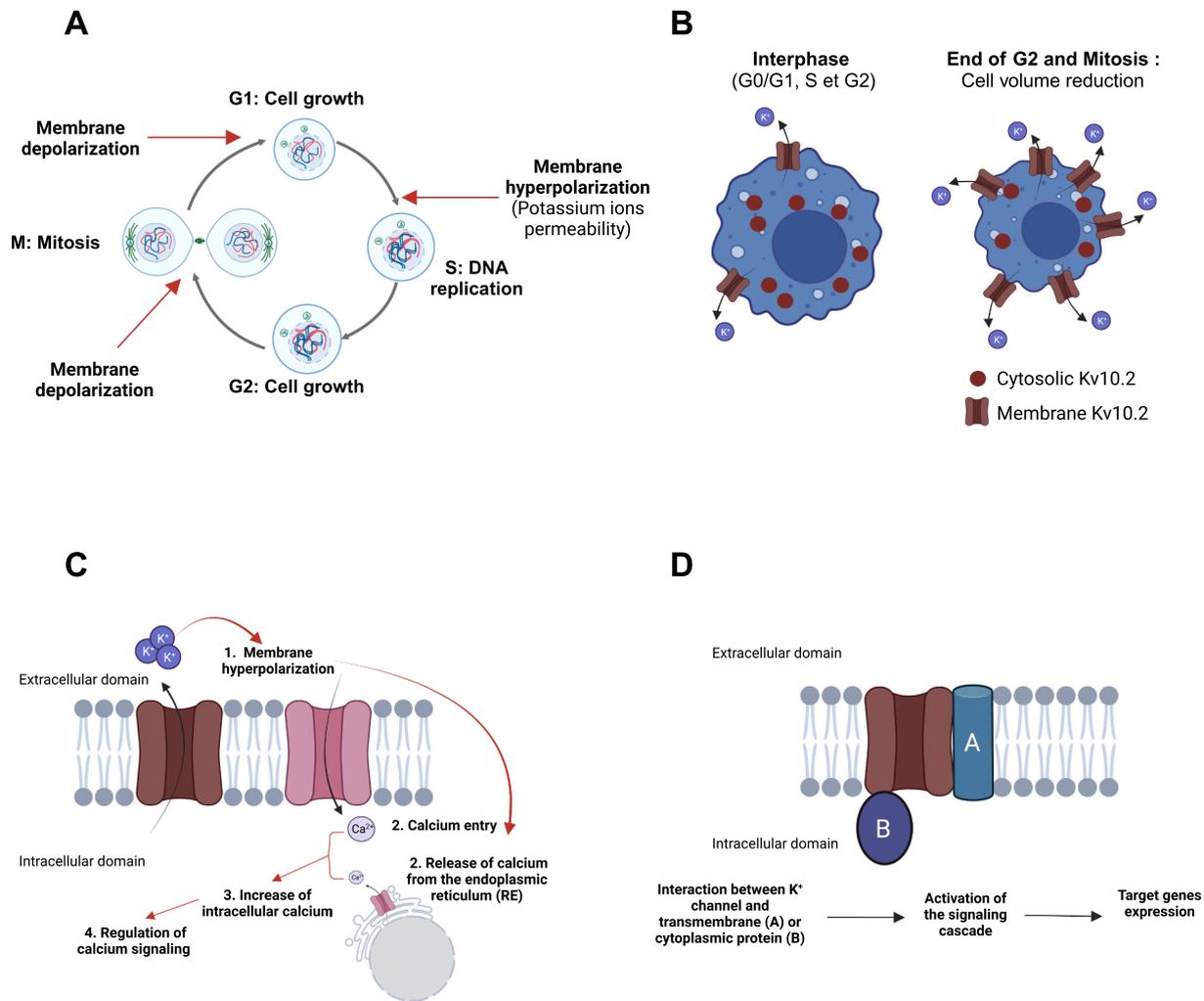


Fig. 2. Mechanisms describing the involvement of potassium channels in the regulation of cell proliferation. (A) Potassium channels are able to regulate the cell membrane polarization, which is modulated through the cell cycle. (B) Potassium channels, and particularly $Kv10.2$, have been shown as regulating the cell volume dynamics during the cell cycle. They promote potassium efflux by being mainly located at the plasma membrane during the end of G2 phase and mitosis, thus enabling cell volume reduction. (C) By hyperpolarizing the plasma membrane (1) with potassium efflux, potassium channels allow an entry of calcium into the cell by increasing the driving force for calcium ions (2), contributing to the increase of intracellular calcium concentration, and thus regulating the calcium signaling, which can promote cell proliferation (3). (D) Via their non-canonical function, potassium channels can promote cell proliferation by interacting with proteins involved in signaling pathways regulating cell proliferation. Based on Huang et al., 2014.

plasma membrane than differentiated cells such as cardiomyocytes or neurons, with a resting membrane potential between -20 and -40 mV (compared to -60 at -80 mV) [50]. Nevertheless, this remains to be further investigated because some differentiated cells have low resting potential while some aggressive cancer cells have hyperpolarized plasma membrane. It has been hypothesized that membrane potential is involved in tumor development, whether it is tumor initiation or progression. Indeed, sustained depolarization generates tumor-like invasion in *Xenopus* embryos [51] and induces DNA synthesis in terminally differentiated central nervous system neurons *in vitro* [52]. As potassium channels are the main actors to regulate the resting membrane potential, they are therefore involved in tumor development. On the other hand, phase-dependent oscillations of the membrane potential have been reported in cancer cell lines as necessary for going through the cell cycle (Fig. 2A). For example, human breast cancer cells (MCF-7) show transient hyperpolarization during the G1/S transition [53], as do neuroblastoma cells, which also show depolarization during the G2/M transition [54] as well as at the end of mitosis, before returning to the G1 phase. In mouse lymphocytes, the transition from quiescence to mitosis is correlated with an initial depolarization followed by a hyperpolarization during DNA replication [55]. This transient membrane hyperpolarization is correlated with 1) increased potassium ion efflux, 2) increased membrane permeability to potassium ions and 3) increased potassium channel activity [54]. And because these changes of membrane potential during cell cycle progression are cell-type dependent [56], a deviation from their physiological membrane potential appears just as important as the depolarization itself. In addition, it was observed that the SK3 potassium channel confers to cancer cells an increase capacity to migrate by hyperpolarizing plasma membrane.

2.2.1.2. Regulation of cell volume. Cell volume regulation also represents a theory which could explain the regulation of cell proliferation by these potassium channels. Cell volume changes is crucial during cell cycle progression. Indeed, volume dynamics studies have described that there is an increase of the cell volume at interphase, then cells condense their cytoplasmic volume before mitosis entry before reaching their minimal volume at metaphase to achieve mitotic rounding and finally end up at increasing their volume to generate the daughter cells [57–58]. Because they generate water flow across cell membrane through potassium flows, potassium channels are central regulators for cell volume. For example, Huang *et al.* have shown a variation in the cellular localization of the Kv10.2 channel (encoding by *EAG2*) depending on the phase of the cell cycle in which medulloblastoma cells are found [59] (Fig. 2B). Indeed, this channel is predominantly cytoplasmic during interphase, but localizes mainly to the plasma membrane at the end of G2 phase and during mitosis, where it is accompanied by greater potassium efflux. This correlates with the reduced cell volume required during mitosis for cell condensation [57]. Silencing of the gene encoding the α -subunit of this channel in medulloblastoma cells leads to an increase in cell volume in G2 phase, followed by cycle arrest during this phase just prior to mitosis [59]. And as expected, the overexpression of *EAG2* in HEK293 cells ends up in constitutive membrane localization of the channel, leading to sustained cell volume reduction and cell cycle impairment and apoptosis eventually [24].

2.2.1.3. Regulation of calcium signaling. Calcium entry pathways differ according to the cell type considered. In electrically excitable cells, calcium influx is mainly mediated by voltage-sensitive calcium channels, which are activated by membrane depolarization [60]. In non-excitable cells, two major calcium influx pathways coexist and differ according to their mode of activation:

- Dependent on intracellular calcium stores, in particular the endoplasmic reticulum (Store-Operated Calcium Entry, SOCE).

- Independent of intracellular calcium stores or Store-Independent Calcium Entry (SICE) (Constitutive Calcium Entry (CCE); arachidonate-regulated Ca^{2+} -selective channels, (ARC); Second Messenger Operated Channels, (SMOC)).

SOCE involves Store-Operated Channels (SOCs), which are mainly members of the TRP (Transient Receptor Potential) and Orai calcium channel superfamilies. It has been shown that the depletion of calcium stores in the endoplasmic reticulum leads to the activation of calcium channels, ultimately resulting in an increase in cytosolic calcium concentration [61] (Fig. 3).

Calcium depletion from the endoplasmic reticulum is initiated by activation of a GPCR (G protein-coupled membrane receptor) or RTK (receptor tyrosine kinase). This activates PLC (phospholipase C), which enables the production of IP3 (Inositol tris-phosphate) from PIP2 (phosphatidylinositol bis-phosphate). IP3 activates its receptor located on the endoplasmic reticulum membrane, ultimately leading to the release of calcium from the endoplasmic reticulum [62]. The action of endoplasmic reticulum Ca^{2+} store emptying causes stromal interaction molecule 1 and 2 (STIM1, STIM2), calcium sensors that loses Ca^{2+} from its N-terminal low affinity EF hand located in the lumen of the endoplasmic reticulum. This causes STIMs to aggregate and to move close to the plasma membrane to physically catch and interact with SOC channels (principally Orais and TRPC1 channels) [63,64–65]. These channels are then activated, allowing calcium to enter the cell.

SICE influx includes SMOC/ARC influx and CCE.

- **SMOCs/ARCs:** Channels can be activated by ligand binding. This is particularly true for cation-permeable P2X channels, which are activated by the binding of their natural ligand, ATP (Adenosine Tri-Phosphate). This activation generates a rapid inward current [66]. Other channels can be activated by an intracellular second messenger. These are known as SMOCs (Fig. 3). Among these channels, ARCs are activated by arachidonic acid (AA) or the AA metabolite leukotriene C4 (LTC 4) and they are composed of both Orai1 and Orai3 proteins which interacts with the pool of STIM1 localized to the plasma membrane [67,68]. With regard to other SMOC channels, PLC also induces DAG (diacylglycerol) formation, leading to activation of TRPC3, TRPC6, TRPV3 or TRPV4 channels [69–71].
- **CCE** is a calcium entry controlled by the electrochemical calcium gradient and that is open/activated in basal condition [72]. The main channels responsible for this calcium influx are the Orai1 channels [73]. This CCE influx can also be initiated by the association of calcium channels with potassium channels. The latter hyperpolarize the plasma membrane by releasing potassium ions out of the cell, thus generating a greater driving force for calcium to enter the cell.

The hyperpolarization of the plasma membrane induced by potassium channel activity leads to an increase in the driving force for various calcium influxes (SOCE, SICE, CCE) (Fig. 2C). Calcium is known to be a crucial second messenger modulating key functions in tumorigenesis. Numerous agonists present in the tumor microenvironment can promote the activation of GPCRs and RTK receptors, leading to IP3 synthesis and calcium release from the ER via IP3 receptors, thereby activating SOCE channels [61]. This leads to an increase in intracellular calcium concentration, which is involved in increased cell proliferation or migration [74,75]. For example, in breast cancer, SOCE, through Orai1 and STIM1, is critical for breast tumor cell migration and metastasis [76]. As mentioned before, Orai1 can also act on CCE influx. It was also demonstrated in breast cancer that Orai1 channel associated with SPCA2 (Secretory Pathway Ca^{2+} -ATPase) can promote CCE and phosphorylation of ERK1/2 (Extracellular signal-regulated kinases) and nuclear translocation of NFAT (Nuclear Factor of activated T-cells) to support cell proliferation increase [73]. The NFAT signaling pathway is therefore activated, inducing cell proliferation [77]. Indeed, it has been

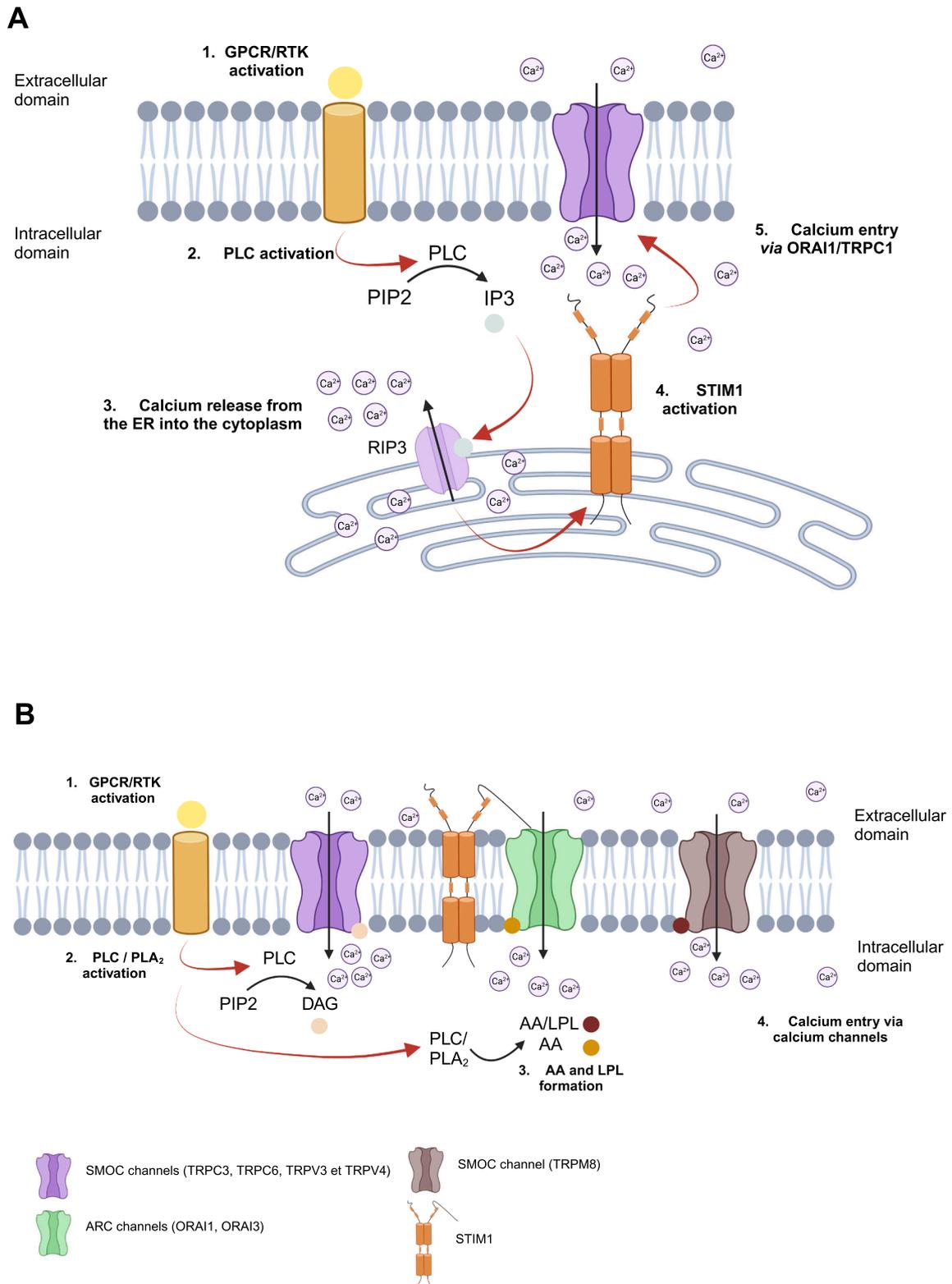


Fig. 3. Schematic description of two types of calcium entries. (A) Calcium can enter the cell according to a SOCE (Store-Operated Calcium Entry) mechanism, dependent of the endoplasmic reticulum (ER). Calcium depletion is triggered by the activation of a GPCR or RTK (1), that activates PLC (2). PLC can produce IP₃ from PIP₂, which activates its receptor on the ER, leading to the release of calcium from the ER (3). This activates STIM1 (and STIM2) channels (4), located on the ER membrane, which concentrate as close as possible to the plasma membrane, interacting with SOC channels, such as ORAI1 and TRPC1, these channels being able to promote calcium entry (5). (B) SMOC/ARC influxes also allow calcium entry according to a SICE (Store-Independent Calcium Entry) mechanism. Briefly, channels are activated *via* ligand binding. The activation of GPCR/RTK (1) allow the activation of PLC/PLA₂. PLC is able to produce DAG from PIP₂, which binds to SMOC channels, allowing calcium entry. PLC and PLA₂ are also able to produce AA and LPL, which bind at ARC (interacting with STIM1 channel) channels and TRPM8, inducing calcium entry.

shown that this signaling pathway is able to regulate various cycle proteins [77], with NFAT2, for example, upregulating cyclin D1 and cyclin D3 expression [78,79]. Furthermore, in breast cancer, NFAT1 induces MDM2 (Murine Double Minute 2) expression and inhibits p53 expression, thus exhibiting pro-proliferative and anti-apoptotic properties [80]. Finally, in pancreatic cancer, NFAT1 inhibits the expression of p15, a tumor suppressor gene [81].

A recent study purposes that SPCA2 also enhances Kv10.1 membrane expression [82], suggesting a triptych model of SICE with Orai1/SPCA2 and Kv10.1. Few years ago, Pardo group described a functional interaction between Kv10.1 and Orai1 that modulates cytosolic calcium oscillations, thereby changing microtubule behavior during cell proliferation [83]. Interestingly, although the mechanisms of action have not yet been fully elucidated, it has been shown that K⁺ channels such as Kv10.1, localized at the centrosome and primary cilium, promote ciliary disassembly and thus Kv10.1-induced cell proliferation *in vitro* and tumor progression *in vivo* [84,85]. Knowing that the cilium is disassembled during cell division, which requires an increase in calcium concentration facilitated by local hyperpolarization, Urrego et al. proposed that Kv10.1 plays a role in coordinating primary cilium disassembly during cell cycle progression *via* localized changes in membrane potential at the ciliary base [86].

2.2.1.4. Non-canonical functions of potassium channels. Potassium channels can interact with various proteins *via* their cytoplasmic domains, therefore explaining their role in the regulation of cell proliferation, bypassing their primary role as ion channels (Fig. 2D). For example, a first study that aimed to transfect both wild-type and nonconducting *Drosophila melanogaster* eag channels into mouse embryonic fibroblasts showed that they displayed the same capacity of proliferation [87]. Other studies proved that the overexpression of non-functional mutants of Kv10.1 [88] and Kv1.3 [89] channels (i.e. nonconducting mutants) promotes cell proliferation and primary tumor growth in cancer mouse models, such as breast cancer mice model. To explain this mechanism, Kv10.1 has been shown to induce angiogenesis by increasing HIF-1 activity and therefore VEGF secretion. Concerning Kv1.3, one of the hypothesis is that its involvement in the regulation of cell proliferation could be the result of its phosphorylation by ERK1/2, thus increasing respiration, driving ROS production and therefore proliferation [90]. Thus, their involvement in the regulation of proliferation might be the result of the activation of a signaling cascade *via* interactions with other proteins, although this mechanism remains partially unknown.

2.2.2. Cell migration and invasion

Various molecular mechanisms may underlie the role of potassium

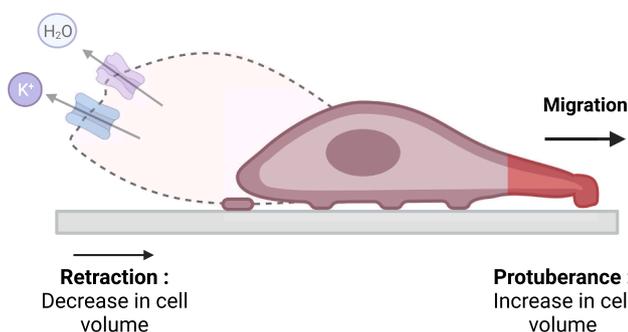


Fig. 4. Involvement of potassium channels in cell migration. During migration, cells undergo cycles of protrusion and retraction. By being located at the trailing end of cells, potassium channels allow potassium efflux, inducing an efflux of water. This mechanism leads to the retraction of the cell, whereas the cell produces a protuberance at the cell front, allowing the cell to migrate. Modified from Schwab et al., 2012.

channels in the regulation of cell migration and invasion.

Cell volume has been shown to be altered during cell migration [91–92]. Indeed, cell migration is a perpetual cycle of cell protrusion and retraction. The cell protrudes at the front, which is characterized by an increase in cell volume, and retracts at the rear, which is associated with a decrease in cell volume [11] (Fig. 4). By being localized at the rear end of the cell, potassium channels allow potassium ions to exit the cell which lead water to exit through aquaporins in order to respect homeostasis, with the ultimate consequence of a reduction in cell volume at this site [11,93]. Potassium channels therefore play a key role in regulating cell migration. This mechanism has been demonstrated for the SK4 channel, where the localized inhibition of this channel by charybdotoxin at the posterior end of renal epithelial cells (MDCK-F) inhibits their migration and increases their cell volume [94].

On the other hand, it has been demonstrated that potassium channels can also modulate cell migration *via* their non-canonical functions. Numerous studies have demonstrated the association of Kv11.1 with integrins (actors in cell adhesion signaling) [95], forming a macromolecular complex involved in cancer cell migration [96], notably in leukemia [97] or melanoma [98–99]. In pancreatic cancer, the activity of the Kv11.1 channel regulates the assembly of F-actin, a cytoskeletal protein, contributing to the formation of pseudopodia, crucial for cell migration [100]. Kv10.1 has also been described to regulate migration and invasion of hepatocellular carcinoma cells *in vitro* and *in vivo*, participating in pseudopod formation *via* regulation of G-actin and F-actin expression [101]. It is also interesting to note that the K_{ir}2.1 channel promotes the metastatic process in osteosarcoma by its interaction with transcriptional factor such as HIF1 α [102] involved in metastasis development [103]. The interaction of K_{ir}2.1 with HIF1 α inhibits its degradation, enabling metastasis both in patients and in mouse models [102]. In addition, among the potassium channels involved in the control of cell migration in hypoxia condition, Kv3.1 and Kv3.4, linked to tumor hypoxia, play a critical role in the migration and invasion of breast cancer cells [104–105].

Finally, potassium channels are also involved in the regulation of cell migration *via* calcium signaling, in various ways. Similar to the above-mentioned process, by hyperpolarizing the plasma membrane, potassium channels are responsible for a higher driving force for calcium entry, in particular *via* the Orai1 calcium channel. This is notably the case for the Kv10.1 channel, in leukemia [106] and breast cancer [107] cells, where its overexpression results in hyperpolarization of the plasma membrane, leading to major calcium entry into these cells. The role of SK_{Ca}-type calcium channels in cell migration will be detailed in chapter 3.5.

2.2.3. Apoptosis

A key step in tumor progression is cell resistance to cell death, such as apoptosis. Apoptosis is in large part controlled by proteins of the Bcl-2 (B-cell lymphoma 2) family, which can be anti-apoptotic, such as Bcl-2 or Bcl-xL (B-cell lymphoma-extra Large), or pro-apoptotic, such as Bcl-10 (B-cell lymphoma/leukemia 10), Bax (Bcl-2-associated X protein) or Bak (Bcl-2 homologous antagonist killer) [108,109].

In the context of tumor cells, several studies have shown that potassium channels increase the expression of anti-apoptotic proteins Bcl-2 and Bcl-XL, and conversely decrease the expression of pro-apoptotic proteins Bax and Bak, thus inhibiting the apoptosis pathway and ultimately tumor cell apoptosis [43]. More specifically, silencing of Kv1.5 induces apoptosis in osteosarcoma cells by decreasing Bcl-2 expression and increasing Bax expression [110]. SK4 also plays an anti-apoptotic role in thyroid cancer [111]. Indeed, silencing of *KCNN4*, the gene encoding the α -subunit of the SK4 channel, decreases Bcl-2 and Bcl-xL expression and increases Bax expression [111]. The role of SK_{Ca}-type potassium channels in cell apoptosis will be detailed in chapter 3.5.

Table 1
SK_{Ca} channels.

| Gene | Locus | Protein | Channel | Transcripts | Protein isoforms |
|--------------|---------|---------------------|---------|--|------------------|
| <i>KCNN1</i> | 19p13.1 | K _{Ca} 2.1 | SK1 | 5 protein-coding transcripts, 2 non-coding transcripts, 1 predicted model of protein-coding transcript | 543 amino acids |
| <i>KCNN2</i> | 5q22.3 | K _{Ca} 2.2 | SK2 | 3 protein-coding transcripts, 2 non-coding transcripts, 3 predicted models of protein-coding transcripts | 579 amino acids |
| <i>KCNN3</i> | 1q21.3 | K _{Ca} 2.3 | SK3 | 5 protein-coding transcripts | 736 amino acids |

3. Small conductance calcium-activated potassium channels

3.1. Nomenclature

Three genes encode the α -subunits of small conductance calcium-activated potassium channels (SK_{Ca}) (Table 1) [29]. They were first identified in 1996, when Köhler *et al.* cloned them from human and rat brain extracts [112].

Although the nomenclature for the calcium-activated potassium channel SK4 (encoded by the gene *KCNN4*) is similar to the channels above, SK4 is not a SK_{Ca} but an intermediate conductance calcium-activated potassium channel (IK_{Ca}), hence, this channel will not be discussed in this chapter.

According to current databases (RefSeq: NCBI Reference Sequence Database), various transcripts are described for each gene, depending on alternative splicing (Table 1). In terms of localization, SK1 is found mainly in neuronal cells, while SK2 and SK3 are ubiquitously localized [113].

3.2. SK_{Ca} channel structure

SK_{Ca} channels are part of the potassium channels formed by 4 α -subunits, themselves composed of 6 transmembrane segments (denoted S1 to S6) and one pore domain, their N-terminal and C-terminal domains being cytosolic [29]. The channel pore is formed by the anchoring of the pore domain of the 4 α -subunits, located between transmembrane segments 5 and 6 [114].

KCNN1, *KCNN2* and *KCNN3* show a high degree of conservation in their nucleic acid sequences and in the protein sequences for the alpha subunits of SK1, SK2 and SK3, with 70–80% homology [112]. This sequence homology between *KCNN1*, *KCNN2* and *KCNN3* is almost perfect at the level of the pore domain, with only 2 different amino acids. Conversely, the sequence of these genes differs mainly in the N-terminal and C-terminal domains, especially in terms of length and sequence [38]. Furthermore, the organization and sequence of these genes are also highly conserved between species: 84% common identity between human and rat *KCNN1* mRNA [115]; 97.6% common identity for *KCNN2* [116] and 94.4% for *KCNN3* [117].

At the C-terminal domain of these α -subunits is localized the calmodulin-binding domain (CaM binding domain, CaMBD), responsible for the sensitivity of these channels to intracellular calcium [118,119], this protein being itself able of binding calcium. More precisely, calcium binding to calmodulin at CaMBD causes a change in channel conformation, initiating channel opening [120]. This binding of calcium ions to calmodulin takes place at “EF-hands” domains, with 4 calcium ions each, forming a helix-loop-helix structure [121]. SK_{Ca} channels sensitivity to intracellular calcium was shown to be modulated

by the phosphorylation state of CaM. Phosphorylation of CaM at Threonine 80 by casein kinase 2, found to be constitutively associated to the C-terminal domain of SK2 and SK3, reduces SK_{Ca} channels calcium sensitivity [122]. Dephosphorylation of CaM by protein phosphatase 2A (PP2A) has the opposite effect [122]. This regulation of SK_{Ca} channels calcium sensitivity through CaM phosphorylation state has been observed on SK2 in cardiomyocytes [123], on SK2 and SK3 in neurons¹²² and on all SK_{Ca} subunits in endothelial cells [124], suggesting a conserved regulatory mechanism.

The importance of this calmodulin-binding domain was first described for IK_{Ca} channels, CaM binding enabling the functional association of the subunits and the recruitment of these channels to the membrane [117]. In the case of SK_{Ca} channels, CaM enables SK2 to be recruited to the plasma membrane [125]. Despite differences in C-terminal sequence homology, this region of CaMBD remains conserved, suggesting a common mechanism of regulation for SK1 and SK3.

It is also interesting to note that other processes may be involved in regulating the subcellular localization of SK_{Ca} channels to the plasma membrane. Indeed, phosphorylation of the SK2 protein at Serine 568, 569 and 570 by cAMP-dependent protein kinase (PKA) has been shown resulting in retention of the channel, preventing it from localizing to the plasma membrane [126], likely through altering CaM binding. These specific phosphorylation sites are not conserved in SK1 and SK3. In addition to the possible regulation of subcellular localization of SK_{Ca} channels, several mechanisms were shown to modulate their activity. SK3 activity has been shown to be reduced by its phosphorylation by PKA, without any alteration of SK3 plasma membrane expression [127]. In pancreatic cancer cells, protein kinase B (Akt) phosphorylates SK2 at Serine 568 and 569, which was shown to increase SK2 sensitivity to calcium, without altering SK2 expression at the plasma membrane [128], contrary to what was observed with the phosphorylation at the same sites by PKA. Acidic conditions have also been shown to reduce SK_{Ca} channels conductance, thus inhibiting SK_{Ca} currents. This effect was shown to occur through the protonation of an outer pore Histidine residue, proposed to exert a repulsive electrostatic effect towards potassium ions [129].

In terms of channel structure, the α -subunits mainly associate to form homotetramers. However, numerous studies have demonstrated the formation of heterotetramers in some cell types, for instance, the association of the SK3 protein with the SK2 and SK1 proteins in HEK cells [130]. In the same study, the authors also observed that the association of SK1 with SK3 caused SK3 to be sequestered in the endoplasmic reticulum, thus preventing SK3 from acting as a plasma membrane channel [130]. A few years later, another study reported the presence of channels formed by an association of the α -subunits encoded by *KCNN1*, *KCNN2* and *KCNN3* in mouse cardiac myocytes [131]. This association of heterotetramers is formed at secondary structures called “Coiled-Coin” domains, located at the C-terminus domains, and identified by crystallization in 2008 [132–133].

On the other hand, SK_{Ca} channels have been discriminated from BK_{Ca} and IK_{Ca} channels based on their electrophysiological and pharmacological properties.

3.3. Electrophysiological properties

K_{Ca} classification is initially based on the value of unitary conductance of their subunits. SK_{Ca} channels are described to have small conductance, between 4 and 14 pS, well below the conductance values of IK_{Ca} and BK_{Ca} channels [112,134]. Furthermore, despite the presence of charged amino acids in the S4 transmembrane segment, these channels are considered to be voltage-independent [135], as the number of these positively charged amino acid residues is not sufficient to confer the voltage-dependent property on these channels [136]. Their activation is therefore not voltage-dependent, but dependent on a sufficient concentration of intracellular calcium.

Their sensitivity to cytosolic calcium being high, they will be

activated by intracellular calcium concentrations below 1 μM , with 50% channel activity when the intracellular calcium concentration is between 400 and 800 nM [120]. A saturation phenomenon can even be observed for intracellular calcium concentrations above 10 μM [120].

SK_{Ca} currents may also present an inwardly rectifying current, thus reducing their already small outward conductance of potassium ions [112,137], which is particularly the case when the membrane potential displays positive values, above + 20 mV [38,120,134]. According to earlier studies, these inward rectifying currents are related to a blockade of channel activity by intracellular cations, on the same principle as K_{ir} channels [138,139]. However, it has recently been suggested that these inward rectifying currents are an intrinsic property of SK_{Ca} channels, independent of the presence of intracellular divalent ions [140]. They showed that some positively charged amino acids in the S6 transmembrane segment, close to the pore, would alter the conductance of SK_{Ca} channels, leading to electrostatic interference [140].

3.4. Pharmacological properties

Numerous chemical compounds modulate SK_{Ca} channels, according to 3 main mechanisms:

- Direct action at the channel pore,
- Modification of channel sensitivity to intracellular calcium concentration,
- Disruption of membrane properties.

These modulators include SK_{Ca} channel inhibitors such as apamin, UCL1684, Edelfosine, Ohmlin, Lei-Dab7 and NS8593, and channel activators such as G542573X and CyPPA. Among the inhibitors, the molecules are differentiated according to their IC_{50} value for each of these channels, while the activators are distinguished according to their EC_{50} value.

3.4.1. Direct action at the canal pore

Such compounds acting directly at the pore of the channel would block all SK_{Ca} channels, depending of course of the bio distribution of the compounds. It would block open or close (use dependent or reverse use dependent action) SK_{Ca} channels in all organs that express SK_{Ca} and thus lack specificity. For example, apamin, a neurotoxic peptide obtained from the venom of the *Apis mellifera* bee [141], acts as a blocker of SK_{Ca} channels, by binding to the loops between transmembrane segments 3 and 4 and 5 and 6 [142]. More specifically, this toxin binds directly to some amino acid residues, including a crucial histidine, located at the channel pore, suggesting an allosteric blocking mechanism [143,144]. This toxin is selective for SK_{Ca} channels, having no effect on BK_{Ca} and IK_{Ca} channels [145]. Its selectivity for the various SK_{Ca} channels differs according to the cell types in which the channels are expressed [146]. Generally speaking, the IC_{50} of apamin is lower for the SK2 channel (30–200 pM) than for SK1 and SK3 channels (8–12 nM and 10 nM respectively) [38], thus showing a specific affinity for SK2, which could be explained by interactions different than those described above. Indeed, apamin also interacts with SK2 and SK3 channels via its positively charged arginine residues (R13 and R14) with the negatively charged aspartate residue (D341) and the neutral asparagine residue (N368), located in the outer pore region of these channels. And, unlike SK2, SK3 channel has only the D341 residue [147].

Other toxins, such as peptide P05, Lei-Dab7 and leurotoxin I, can also act as blockers for SK_{Ca} channels [148–149].

UCL1684 is also a potent inhibitor of SK_{Ca} channels, binding to the channel, and having a particular affinity for SK1 and SK2 channels rather than SK3, with IC_{50} of 800 pM, 200 pM and 10 nM respectively [38,150].

3.4.2. Modification of channel sensitivity to cytosolic calcium concentration

A second mechanism for the regulation of SK_{Ca} channels involves

modulating their sensitivity to calcium. These modulators of calcium sensitivity would gain in specificity and especially in cancer. Indeed, it has been found that some cancer cells have high cytosolic concentration of calcium [151] compare to non-cancer cells. Compounds that decrease calcium sensitivity of SK_{Ca} would decrease SK_{Ca} activity mostly in cells having high cytosolic concentration of calcium compare to other cells. In parallel, it has been demonstrated that in cancer cells, SK_{Ca} are not expressed alone in plasma membrane and mostly as onco-complexes of calcium and SK_{Ca} channels [152]. Thus, compounds that decrease calcium sensitivity of SK_{Ca} would decrease SK_{Ca} activity that are expressed in these onco-complexes.

CyPPA was the first SK_{Ca} channel activator described to act according to this mechanism, with an EC_{50} in the micromolar range for SK2 and SK3 channels ($\text{EC}_{50}(\text{SK2}) = 14 \mu\text{M}$, $\text{EC}_{50}(\text{SK3}) = 6 \mu\text{M}$), but with no effect on SK1 [153]. This activator induces a leftward shift in calcium activation curves for the SK3 channel, and to a lesser extent for SK2 [153]; these channels are thus activated by lower intracellular calcium concentrations. Its mechanism of action goes through its binding to CaMBD [142].

This is also the case for GW542573X, which is a particularly specific activator of SK1 [154]. It can modulate this channel sensitivity by interacting with amino acids at the S5 transmembrane segment [142]. Its EC_{50} for SK1 is around 8.2 μM , making it 10 times more specific than for SK2 and SK3 [38]. As with CyPPA, GW542573X shifts the calcium activation curve to the left, with the calcium response curve for SK1 changing from 410 nM to 240 nM at 10 μM activator concentration [154].

Few inhibitors using this mechanism have been identified. However, NS8593 was the first modulator to reduce negatively the calcium sensitivity of SK_{Ca} channels [155]. It shifts the calcium activation curve to the right, increasing the intracellular calcium concentrations required to activate these channels. Although it is not selective for any particular SK_{Ca} channel, it is inactive for most other ion channels, including BK_{Ca} channels [38,155].

3.4.3. Disturbance of membrane properties

A third mechanism of action for SK_{Ca} channels modulators has been described more recently. Edelfosine, an anti-tumor compound, was first shown to inhibit SK3 channel function at low calcium concentrations, below 1 μM [151]. Due to its structure, the hypothesis of this compound's integration into membranes was prioritized. Indeed, Edelfosine can be incorporated into membranes close to the channels, which, thanks to their transmembrane segments, would sense changes in the lipid environment [156], thus influencing their activity. In addition, Edelfosine is able to modify the supramolecular arrangement of membranes, which also regulates the activity of SK_{Ca} channels [157].

Based on the same operating principle, Ohmlin, a synthetic alkyl-ether-lipid, has also been studied for its SK_{Ca} channel modulatory properties [158]. This is the first inhibitor capable of discriminating between SK1 and SK3 channels and SK2, having no effect on the latter and a particular affinity for SK3, with an IC_{50} of around 300 nM [158]. Ohmlin acts through its incorporation in enriched cholesterol nano-domain named lipid rafts [159]. Ohmlin dissociates onco-complexes of calcium and SK_{Ca} channels expressed in cancer cells. The delocalization of SK3 outside lipid rafts is sufficient to decrease its activity without blocking the pore of the channel. SK3 channel is mostly expressed in lipid raft because of its high interaction with cholesterol and Ohmlin compete with cholesterol to bind the channel thus conferring a selectivity for SK3 channel [160]. In addition, Ohmlin changes the biophysical of membrane, what was reported to be associated with aggressiveness in terms of cell motility and migration, leading to metastasis formation [161].

3.5. Expression and function of SK_{Ca} channels in tumor cells

Numerous studies have reported the overexpression of SK_{Ca} channels

in tumor cells, the very first study having reported overexpression of *KCNN3* in medulloblastoma cells, although this overexpression was not associated with a precise biological function [162]. In general, overexpression of *KCNN2* and *KCNN3* has been observed in tumor cells from breast cancer [163], melanoma [164,165] and prostate cancer [166,167].

In most studies, overexpression of *KCNN2* and *KCNN3* was associated with a key tumor development process, making these channels potential targets for anti-tumor therapies [168,169]. For example, *KCNN2* has been shown to be involved in the regulation of cell proliferation in melanoma cells under hypoxic conditions [165]. In pancreatic cancer, an increase in *KCNN2* expression was observed in metastases versus primary cancers as well as in more aggressive molecular subtypes and SK2 activation was shown to contribute to cancer aggressiveness [128]. Numerous studies have targeted *KCNN3*, showing that SK3 is involved in the migration of breast, prostate, melanoma, colon and bladder tumor cells [163,164,167,170–172]. More precisely, the SK3 channel also promotes migration of prostate and breast cancer tumor cells (Fig. 5) by increasing calcium entry through the formation of a complex with Orail1 [159], regulated by a chaperone protein, SigmaR1 [170]. Another cancer hallmark is promoted by SK_{Ca} channels. As SK2 and SK3 channels participate to the resistance of apoptosis, their silencing decreasing Bcl-2 expression and increasing caspase 7 and 9 expression, the activation of the latter activating apoptosis in breast cancer cells [173].

Considering SK1 channel, only one study has identified *KCNN1* expressed in cancer cells, specifically in Ewing sarcoma cells [174], without any link to biological function associated to tumor development.

4. Voltage-gated potassium channels

4.1. Nomenclature

As mentioned in Chapter 2, voltage-gated potassium channels are one of the most diverse families of potassium channels. This family of potassium channels is classified into 12 subfamilies, including the “Shaker-related” potassium channel subfamily, on which we will focus. This name originates from the “Shaker” channels first observed in *Drosophila* [29,175]. Eight genes encode the α -subunits of these potassium channels (Table 2) [29]. These genes were initially identified in the

Table 2
Kv1 channels.

| Gene | Locus | Channel | Transcripts | Protein isoforms |
|---------------|----------|---------|---|------------------|
| <i>KCNA1</i> | 12p13.32 | Kv1.1 | 1 protein-coding transcript | 495 amino acids |
| <i>KCNA2</i> | 1p13.3 | Kv1.2 | 2 protein-coding transcripts 4 predicted transcripts | 499 amino acids |
| <i>KCNA3</i> | 1p13.3 | Kv1.3 | 1 protein-coding transcript, 2 non-coding transcripts | 575 amino acids |
| <i>KCNA4</i> | 11p14.1 | Kv1.4 | 1 protein-coding transcript | 653 amino acids |
| <i>KCNA5</i> | 12p13.32 | Kv1.5 | 1 protein-coding transcript | 613 amino acids |
| <i>KCNA6</i> | 12p13.32 | Kv1.6 | 1 protein-coding transcript, 3 non-coding transcripts, 3 predicted transcripts models | 529 amino acids |
| <i>KCNA7</i> | 19q13.33 | Kv1.7 | 1 protein-coding transcript | 456 amino acids |
| <i>KCNA10</i> | 1p13.3 | Kv1.8 | 1 protein-coding transcript | 511 amino acids |

early 1990s, including *KCNA2*, cloned for the first time in mammals in 1994 [176].

As SK_{Ca}, various transcripts are described for each gene, according to current databases (RefSeq; NCBI Reference Sequence Database) (Table 2). Kv1 channels are mainly found in the nervous and central systems, as well as in the heart [177–179]. However, some channels are also localized in other tissues [25], as in the case of Kv1.1 expressed in the kidney [180], Kv1.3, ubiquitously expressed in the body, Kv1.4, which is also localized in the intestinal tract [181], or Kv1.5 and Kv1.6, which may be expressed in the colon [181].

4.2. Kv1 channel structure

Kv1 channels belong to the potassium channel family whose α -subunits are composed of 6 transmembrane segments (S1 to S6) and a pore domain. Their N-terminal and C-terminal domains are also cytosolic [29]. They assemble into tetramers of α -subunits to form active channels, the channel pore being formed by the loop located at the pore domain between transmembrane segments S5 and S6 of each α -subunit [182].

One study based on a comparison of potassium channel-coding genes

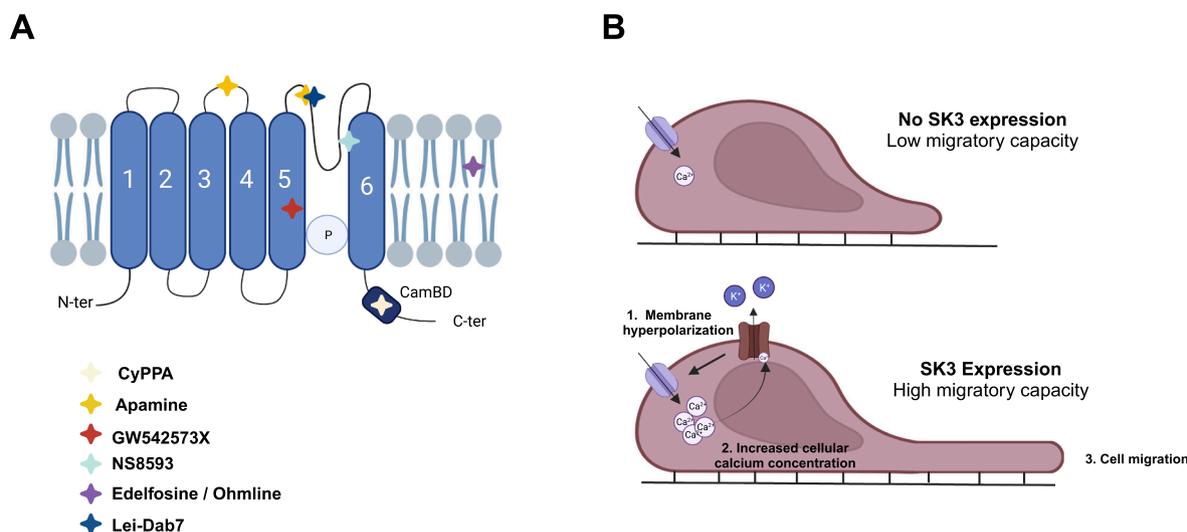


Fig. 5. SK_{Ca} channels in cancers. (A) Structure of the α subunit of SK_{Ca} channels, composed of 6 transmembrane segments and one pore domain. Various modulators can inhibit or activate SK_{Ca} channel activity by binding directly at the canal pore, at the CamBD or by perturbing plasma membrane properties. (B) Involvement of SK3 channel in the cell migration in breast cancer cells. When SK3 is expressed at the plasma membrane, it induces a membrane hyperpolarization (1), inducing a higher driving force for calcium ions, thus increasing the intracellular calcium concentration (2), allowing the cell to migrate.

suggests a common origin of the K_{ir} , Kv and K2P potassium channels [183]. Within the “Shaker-related” channel family, significant sequence homology has been observed, particularly in the pore domain, known to play a major role in the selectivity of potassium channels [184]. Indeed, one of the most conserved regions of these channels is located at the S6 transmembrane segment, with the signature sequence Proline - X - Proline (X representing any amino acid), characteristic of these channels, playing a crucial role in channel opening [182]. More precisely, according to the total number of amino acids forming the respective proteins and sequence alignment at the pore domain, the Kv1.1 and Kv1.2 channels show almost perfect sequence homology, with 5 different amino acids, as do Kv1.4 and Kv1.5 [185]. The sequences of Kv1.3 and Kv1.6 differ by 7 amino acids in the pore domain [185]. In addition, the domains allowing tetramerization of the α -subunits are also highly conserved, with 77% sequence homology between Kv1.1-Kv1.6, and even 93% homology between Kv1.2 and Kv1.3 [186].

The S4 transmembrane segment is responsible for the voltage sensitivity of voltage-gated potassium channels. Indeed, this domain contains the Voltage Sensor Domain (VSD), which is similar to other voltage-gated ion channels such as voltage-gated sodium and calcium channels [187]. More precisely, the sequence of this S4 transmembrane segment contains, depending on the Kv channel, 4 to 7 repeating motifs of three amino acids, the first being positively charged (often an arginine) followed by two hydrophobic amino acids [188,189]. The Kv1.2 channel, for example, is composed of 6 repeats of this motif [190]. The presence of these positively charged amino acids is responsible for the voltage sensitivity of Kv channels. Indeed, they are able to sense the electric field, thus modifying the conformation and activation of the channel according to variations in membrane polarity [191].

Post-translational modifications can also occur, modifying the properties of Kv1 channels. For example, phosphorylation of the Kv1.3 channel at Tyrosine 135 modulates its role in neuroinflammation in Parkinson's disease [192]. Furthermore, sumoylation of the Kv1.5 channel leads to its inactivation in atrial myocytes [193]. Another study reported that the palmitoylation of the Kv1.5 channel at a cysteine (C593) located at its C-terminal domain increases its internalization and thus decreases its activity at the plasma membrane in an *in vitro* model of CHO (Chinese Ovary Hamster) cells [194].

As SK_{Ca}, Kv channels, and especially Kv1 channels, can be found as both homotetrameric and heterotetrameric forms. In example, the α -subunit of Kv1.2 is known to interact with Kv1.1 [195], or Kv1.5 [196], forming heteromeric complexes. Heteromeric complexes can also be formed with regulatory subunits. This is the case for the α subunit encoded by *KCNA2*, which has been shown to interact with two β -regulatory subunits, *KCNA β 1* and *KCNA β 2* [197].

Due to their structure, Kv channels also exhibit their own electrophysiological and pharmacological properties.

4.3. Electrophysiological properties

As their names indicate, Kv1 potassium channels are voltage-gated channels. They are activated following membrane depolarization, in order to repolarize the membrane, *via* the efflux of potassium ions [198]. This activation is notably enabled by the presence of positively charged amino acids sensing the change in polarity as described in the previous chapter. This electrophysiological property gives these Kv the ability to control both the resting membrane potential and the duration and frequency of action potentials [199].

Most Kv1 channels have a low activation threshold and activate rapidly. Moreover, with the exception of Kv1.4, which has a rapid inactivation current, all channels of the Shaker-related family have slow inactivation and delayed-rectifier potassium currents [176,200,201]. This implies that these channels allow potassium ions to pass the pore with a delay following membrane depolarization [202].

As already mentioned, the α -subunits are also able of interacting with β -subunits, known as regulators. There are 3 β -subunits, which are able

to bind to the N-terminal of the α -subunits, thereby regulating channel activity, including inactivation [182,190]. Thanks to its “ball and chain” structure, the β -subunit can be inserted into the pore of the channel, leading to its blockade and inactivation [203–205].

4.4. Pharmacological properties

4.4.1. Inhibitors

Most known inhibitors of Kv1 channels are toxins derived from venomous animals. Dendrotoxins, derived from the venom of a mamba snake, were the first inhibitors of Kv1 channels, making it possible to purify the Kv1 channels binding to these toxins (Kv1.1, Kv1.2 and Kv1.6) from bovine brains [206]. Other toxins are also well known and frequently used in research, such as margatoxin, a specific inhibitor of Kv1.3, or charybdotoxin, derived from scorpion venom, which is a non-specific inhibitor of Kv1.2 [207], but also of Kv1.3 and SK4 [208,209]. It is also possible to emphasize agitoxin-1 and kaliotoxin [210,211], which inhibit Kv1 channels in the same process. Concerning Kv1.5, two peptides derived from the venom of tarantula and scorpion are known in the literature [212]: Osu1 and Ts6. In fact, these Kv1 channel inhibitors are pore blockers, acting as a “plug” at the active channel. Most of these toxins share an amino acid sequence consisting of a positively charged lysine and a hydrophobic amino acid (tyrosine or phenylalanine) [213,214]. The lysine can then insert itself into the channel's selectivity sensor, while the hydrophobic amino acid anchors the toxin's binding to the channel.

More recently, new toxins have been identified from sea products [215]. Nine conotoxins have been described as inhibitors of Kv1 channels [216], acting according to the mechanism described above. Most of these conotoxins target Kv1.2, including the Y family of conopeptides (CPYs), with CPY-P11 [217] and κ M-R11J [217], with IC₅₀ of 2 μ M and 33 nM respectively for Kv1.2. Among sea toxins, cnidarian peptides have also been identified, produced by sea anemones [218]. These inhibitors belong to the family of non-enzymatic neurotoxic peptides, divided into 9 categories according to their structures [215]. Among these toxins, BcsTx3 was isolated from the sea anemone *Bunodosoma caissarum* [219]. This toxin is able to inhibit the activity of Kv1.1, Kv1.2, Kv1.3 and Kv1.6 channels by binding to their extracellular domains. Their mechanism of action is different from that explained above, as it does not present the amino acid dyad cited [215].

Finally, there are also non-peptide inhibitors, such as Aplysiatoxins from marine cyanobacteria, able to inhibit Kv1.5 channels [220]. Indeed, these compounds display minimal side effects concerning the blockade of Kv1.5 in atrial tachyarrhythmias [221].

Two possible mechanisms of action have been described for this group of toxins. They could be direct blockers of the channel pore, or act according to an indirect mechanism of action, *via* activation of protein kinase C [222].

Some of these inhibitors are now being used *in vitro* to test their potential anti-tumor effect. Examples include amiodarone, a Kv1.3 inhibitor in prostate cancer [223], and verapamil, also a Kv1.3 inhibitor (initially a calcium channel inhibitor), which has been tested in melanoma [224] and prostate cancer [225], as well as Psora-4, an inhibitor of both Kv1.3 and Kv1.5 used in lymphoma [226].

4.4.2. Activators

Kv1 channel activators have been less studied and described. One of the only studies concerns a large family of warfarin-related compounds [227]. These Kv1.5 activators are able to bind to two pockets located between the sensor domain and the channel pore, thereby stabilizing the sensor domain/channel pore coupling in the open state. Other Kv channel activators exist, however, targeting Kv7.2 [228,229] for example, and acting either at the sensor domain or directly at the channel pore. It is also possible to cite the RPR260243 compound, which is a specific inhibitor of the Kv11.1 channel, having shown its effect in the treatment of arrhythmia in a zebrafish model [230] or the NS3623

compound, known to be an activator of both Kv11.1 and Kv4.3 [231].

4.5. Expression and function of Kv1 channels in tumor cells

Various studies have reported aberrant expression of Kv1 channels in different types of cancers. In particular, 4 Kv1 channels have been mainly studied: Kv1.1, Kv1.3, Kv1.4 and Kv1.5 [25].

KCNA3 and KCNA5 expression correlates with survival in patients with squamous lung cell carcinoma and stomach adenocarcinoma respectively [232]. Furthermore, overexpression of these channels is associated with deregulation of a “cancer hallmark”, whether cell proliferation, migration or apoptosis [25]. KCNA1, for example, is overexpressed in medulloblastoma [233], cervical cancer, where its overexpression deregulates the aforementioned cellular processes by impacting mitochondrial function [234]. KCNA3 is overexpressed in many tumors [25], such as, for example, human skeletal muscle sarcoma [235], leiomyosarcoma [236], glioblastoma [237] and melanoma. The use of specific inhibitors of this channel has disrupted its interaction with β 1 integrin, suggesting its role in cell adhesion and invasion [224]. Kv1.3 is increasingly being studied for its potential targeting in cancer [238,239]. Indeed, in chronic lymphocytic leukemia, targeting mitochondrial Kv1.3 with pharmacological agents induces apoptosis in these tumor cells [240]. As for Kv1.4, its overexpression has also been observed in neuroblastoma cells [241], impacting the cell cycle. Finally, Kv1.5 is the most studied channel in tumor cells, where it has been observed to be overexpressed in many tumors such as glioma [242] astrocytoma or oligodendroglioma [25]. This overexpression of Kv1.5 correlates with degrees of malignancy, and in gastric cancer, this channel is implicated in the regulation of tumor cell proliferation [243], or even in smooth muscle sarcomas [235].

5. Conclusion

This overall review suggests that potassium channels, particularly those with 6 transmembrane segments and a pore domain such as SK_{Ca} and Kv1, could be a relevant therapeutic target in cancer. Some of these channels are indeed involved in the control of key tumor development functions such as cell proliferation, cell migration and cell death. It is easy to hypothesize that by controlling these functions, these structures play a part in controlling primary tumor growth and metastatic progression. In this context, an ongoing Phase II clinical trial (ClinicalTrials.gov No NCT 03954691) aims to test the hypothesis that targeting the calcium-activated potassium channel SK4 and the voltage-dependent potassium channel Kv1.3 could be a valuable therapeutic strategy for reprogramming cells of the innate immune system, with the aim of combating glioma, a lethal tumor of the central nervous system (CNS). Thus, this review proves the importance of better understanding the role of potassium channels in tumor development and the relevance of targeting them in cancer, in particularly SK_{Ca} and Kv1 channels.

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CRediT authorship contribution statement

Maryne Dupuy: Writing – original draft. **Maxime Gueguinou:** Writing – review & editing. **Marie Potier-Cartreau:** Writing – review & editing. **Frédéric Lézot:** Writing – review & editing. **Marion Papin:** . **Aurélien Chantôme:** Writing – review & editing. **Françoise Rédini:** Writing – review & editing. **Christophe Vandier:** . **Franck Verrecchia:** Writing – original draft, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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