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Review

Store-independent Orai1-mediated Ca^{2+} entry and cancer

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ABSTRACT

Ca^{2+} channels play an important role in the development of different types of cancer, and considerable progress has been made to understand the pathophysiological mechanisms underlying the role of Ca^{2+} influx in the development of different cancer hallmarks. Orai1 is among the most ubiquitous and multifunctional Ca^{2+} channels. Orai1 mediates the highly Ca^{2+}-selective Ca^{2+} release-activated current (I_{CRAC}) and participates in the less Ca^{2+}-selective store-operated current (I_{SOC}), along with STIM1 or STIM1 and TRPC1, respectively. Furthermore, Orai1 contributes to a variety of store-independent Ca^{2+} influx mechanisms, including the arachidonate-regulated Ca^{2+} current, together with Orai3 and the plasma membrane resident pool of STIM1, as well as the constitutive Ca^{2+} influx processes activated by the secretory pathway Ca^{2+}-ATPase-2 (SPCA2) or supported by physical and functional interaction with the small conductance Ca^{2+}-activated K^+ channel 3 (SK3) or the voltage-dependent $K_v10.1$ channel. This review summarizes the current knowledge concerning the store-independent mechanisms of Ca^{2+} influx activation through Orai1 channels and their role in the development of different cancer features.

1. Introduction

Orai1 and its two mammalian homologs, Orai2 and Orai3, have been reported to form Ca^{2+}-selective ion channels that mediate Ca^{2+} influx upon cell stimulation [1,2]. Orai channels exhibit four transmembrane domains, which are connected with two extracellular and one intracellular loop, and N- and C-termini facing the cytosol [3]. Orai proteins, in particular Orai1, show different functional domains in the N- and C-termini that are crucial for the interaction of these proteins with their partners and modulators, including STIM proteins [4–6] but also SARAF (store-operated Ca^{2+} entry (SOCE)-associated regulatory factor), adenylyl cyclase 8 or CRACR2A (Ca^{2+}-release activated Ca^{2+} (CRAC) regulator 2A), among others [7–9].

Orai1 has been clearly implicated in SOCE in most cell types. In particular, Orai1 is a constituent of two different store-dependent Ca^{2+} channels: the CRAC channel, a hexameric Orai1 structure that conducts the highly Ca^{2+} selective and inwardly rectifying I_{CRAC} current [10–12], and the less Ca^{2+} selective store-operated Ca^{2+} (SOC) channels, which involve Orai1 and TRPC1 subunits [13–16]. While the role of Orai1 in SOCE has been widely characterized, the precise physiological role of Orai2 and Orai3 channels remains unclear. We have evidenced that Orai2 plays a key role in SOCE in the human HL60 promyeloblastic cell line [17]. On the other hand, Orai3 has been implicated in SOCE in a limited number of cell types, including the estrogen receptor positive (ER^+) breast cancer cell lines [18,19], and prostate epithelial and tumoral cells [20].

In addition to the involvement of Orai1 in SOCE, this protein has been found to play a key role in different store-independent Ca^{2+} entry (SICE) pathways. Among them, Orai1 participates in the Ca^{2+} currents activated by arachidonic acid (AA) or the AA metabolite leukotriene C4 (LTC4), along with Orai3, through the so called arachidonate-regulated or LTC4-regulated Ca^{2+} channel (ARC/LRC) [21,22]. Furthermore, Orai1 has been found to mediate SICE in the mammary gland during lactation as well as in a number of breast cancer-derived cells and human breast tumors following up-regulation of the secretory pathway Ca^{2+}-ATPase, SPCA2 [23,24]. The activation of Orai1 by SPCA2 is independent of the ATPase activity of SPCA2 [24]. Studies performed in three-dimensional cultures of normal mouse mammary epithelial cells, called mammospheres, have revealed that SPCA2 is required for Orai1 trafficking to the plasma membrane and both, SPCA2 and Orai1, are required for Ca^{2+} influx and mammosphere differentiation [25]. A third mechanism for SICE mediated by Orai1 has been reported in

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native and tumoral cells that exhibit a physical and functional interaction between Orai1 and the small conductance Ca^{2+}-activated K^+ channel 3 (SK3). In cancer cells, SK3 channel has been found to control constitutive Ca^{2+} entry by interaction with Orai1, which is required for cell migration [26], while in gallbladder smooth muscle cells, Ca^{2+} entry *via* Orai1 has been shown to activate SK3, leading to membrane hyperpolarization, which, in turn, prevents excessive contraction of gallbladder smooth muscle in response to physiological agonists [27]. A more recent report has revealed a functional interaction between Orai1 and the EAG family member $K_v10.1$ channel in breast cancer cells. Co-localization between Orai1 and $K_v10.1$ might allow the latter to enhance the basal Ca^{2+} entry through Orai1, thus resulting in the activation of ERK1/2 and cell survival [28].

In this review we summarize the current knowledge concerning the Orai1-mediated SICE mechanisms and their involvement in the development of different cancer features.

2. ARC channel function and cancer

The concept of ARC emerged in 1996, based on a series of studies using low agonist concentrations that identified a mechanism for Ca^{2+} entry that exhibited properties different from the well-known currents of the SOCE model [29]. Even, different authors have shown antagonistic roles of SOCE and AA-evoked Ca^{2+} entry [30–32]. ARC channels have been reported to consist of three Orai1 and two Orai3 subunits with the participation of the plasma membrane resident STIM1 [33,34]. Thompson and coworkers have described that the N-terminus of Orai3 is required for the activation of ARC channels by AA [35], although the precise mechanism of ARC channel gating by AA remains unsolved. A more recent study by Zhang and coworkers have evidenced a specific interaction of the second coiled-coil domain (CC2) of STIM1 with the Orai3 C-terminal region, which seems to be required for LRC channel activation [36].

ARC channels show biophysical properties that differ from that reported for CRAC channels or receptor-operated TRPC channels. Among these features, ARC channels are not activated by diacylglycerol (100 μM) [37], do not show the CRAC-typical fast Ca^{2+}-dependent inactivation, are insensitive to 2-aminoethoxydiphenyl borate and are not inhibited by low extracellular pH [38,39].

ARC channels are regulated by SARAF, which negatively modulates Ca^{2+} influx evoked by AA [40]. SARAF is a STIM1 regulator that prevents spontaneous SOCE activation and mediates slow Ca^{2+}-dependent inactivation [41–43]. We have recently reported that the interaction of SARAF with STIM1 is modulated by the Ca^{2+}-binding protein EFHB (EF-hand domain family member B, also known as CFAP21), which allows SARAF-STIM1 dissociation in order to activate Orai1 channels [44]. SARAF was initially identified as a SOCE regulatory ER-resident protein but it is also expressed in the plasma membrane in a manner dependent on the surface expression of STIM1 [45].

There is a growing body of evidence reporting a role for altered Ca^{2+} homeostasis in the support of a variety of cancer hallmarks, including dysregulated cell proliferation, migration or apoptosis resistance [46–48]. Compared to SOCE, little is known about the role of the AA-induced Ca^{2+} signals in cell function and their contribution to disease, including cancer. The association of two exclusive mammalian [49,50] proteins, Orai1α and Orai3, to form ARC channels likely constitutes a highly specialized mechanism that mediates cellular responses. The upregulation of Orai1 and Orai3 observed in various disorders suggests the potential role of ARC channels in the pathogenesis of different diseases [51].

Studies in airway smooth muscle (ASM) cells isolated from asthmatic individuals have revealed that AA-activated ARC currents are significantly greater than in ASM cells of healthy subjects, suggesting that ARC channels could potentially contribute to dysregulated Ca^{2+} signaling in diseases such as asthma [52]. Furthermore, Saliba and coworkers have reported that adult cardiomyocytes exhibit a Ca^{2+}-permeable conductance activated by AA, mediated by Orai3, and regulated by STIM1, that is increased during cardiac hypertrophy [53]. Similar observations have been found during vascular smooth muscle remodeling *in vivo*, especially in vessels of rats subjected to balloon angioplasty [54,55]. In these studies, Orai3 knockdown prevented Orai3 upregulation, inhibited LRC/ARC currents, and decreased neointima formation after vascular injury [54,55]. In addition, these findings reported that Orai3 promotes migration but has not a role in cell proliferation. This is opposite to the findings reported for STIM1 and Orai1-mediated SOCE, which is involved both in proliferation and migration [17,55,56]. These findings indicate that LRC-mediated Ca^{2+} entry in VSMCs might be associated to different or, at least, more restricted downstream signaling pathways than SOCE.

A recent study reported that AA-induced Ca^{2+} entry is the dominant Ca^{2+} entry pathway regulating migration of the gastro-enteropancreatic neuroendocrine tumor BON cell line. In addition, both Orai1 and Orai3, were found to be required for AA-mediated Ca^{2+} entry [57]. Although, Goswamee et al. did not directly test whether LTC4 could activate Ca^{2+} entry or cell migration in their system, pharmacological inhibition of AA-metabolism did not suppress AA-induced BON cell migration. This indicated that the enhancement of cell migration observed was largely due to AA itself and not its metabolites.

In prostate cancer cells, Prevarskaya's group has reported that remodeling of Orai channel expression determines an oncogenic switch. In particular, Orai3 overexpression leads to the formation of store-independent AA-regulated channels, to the detriment of SOCE channels. This phenotypic switch has been shown to be involved in cell progression to a more aggressive pro-proliferative phenotype and promotes apoptosis resistance by attenuating the participation of Orai1 in the formation of CRAC/SOCE channels, which confers susceptibility to apoptosis in these cells [58].

Fiorio Pla and coworkers reported that low concentrations of AA are able to evoke Ca^{2+} influx exerting a mitogenic role in bovine aortic endothelial cells (EC) and tumoral angiogenesis [59]. AA and its metabolic derivatives have long been known to promote *in vitro* EC proliferation, migration and tubulogenesis [60,61]. Despite a number of studies have evidenced that EC proliferation is the result of an increase in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) [62,63], the expression of Orai1/Orai3-based ARC channels in ECs has not been demonstrated yet and deserves further studies.

3. Ca^{2+} entry by the Orai1/SPCA2 pathway and cancer

In eukaryotes, Ca^{2+} homeostasis is finely modulated by a variety of channels and transporters that control the intracellular levels of the ion. Among the transporters, the role of the plasma membrane Ca^{2+}-ATPase (PMCA) and the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) in the clearance of cytosolic Ca^{2+} has been characterized; however, the function of the SPCA in Ca^{2+} homeostasis remains unclear. SPCA proteins sequester Ca^{2+} and Mn^{2+} from the cytoplasm into the Golgi lumen and its vesicles where they are required for posttranslational processes, such as glycosylation, and protein sorting [64,65].

Two SPCA isoforms, SPCA1 and SPCA2, have been described in eukaryotic cells [66,67]. Whereas SPCA1 is ubiquitously expressed among cell types and eukaryotic organisms, ranging from yeast to human, SPCA2 is just present in higher eukaryotes, including human, and in a limited amount of tissues, such as the gastrointestinal or genitourinary tracts, nervous system, lungs and testis, as well as in mammary, thyroid and salivary glands [25,66,67].

Due to the similarities between SPCA1 and SPCA2, both in structure and function, and their differential expression among eukaryotes, the latter was initially believed to exert a redundant function in the cell [66,68]. However, this concept changed after the report of Faddy and coworkers demonstrating that the expression of SPCA2 increased by 35-fold during lactation (as compared to SPCA1 expression that barely increased 2-fold) and was mainly located in the luminal secretory cells

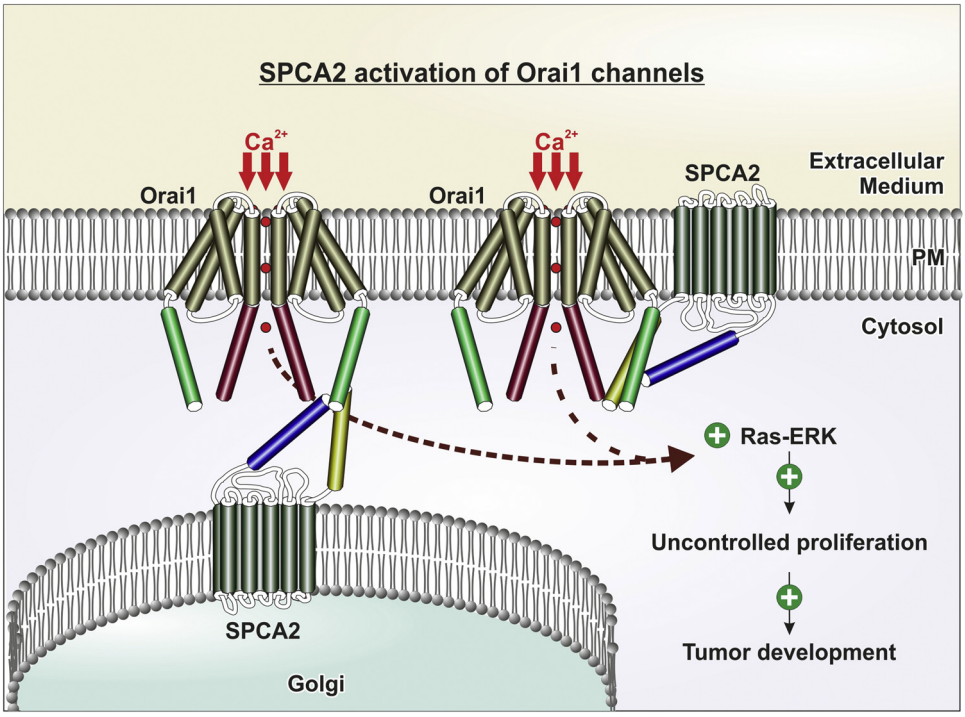

Fig. 1. Ca^{2+} entry by the Orai1/SPCA2 pathway. SPCA2 located in the plasma membrane or the intracellular vesicles/Golgi induces constitutive Ca^{2+} entry through Orai1 channels, which leads to the activation of the Ras–ERK pathway and results in exacerbated cell proliferation.

of the mammary gland [23]. Consistently, a more recent study by Smaardijk and coworkers have revealed that SPCA2 evokes Ca^{2+} influx *via* orai1 and promotes Ca^{2+} uptake to the Golgi/secretory pathway, a process that might be physiologically relevant in secreting cells, such as mammary acinar cells during lactation [69]. Furthermore, Rao's group found that SPCA2 was able to activate constitutive Ca^{2+} entry, mediated by Orai1, in the luminal MCF7 breast cancer cell line [24]. The rise in $[Ca^{2+}]_i$ mediated by the complex SPCA2–Orai1 leads to the activation of the Ras–ERK pathway, involved in cell cycle and proliferation [70], and whose hyperactivation has been described in a number of human cancers [71].

The association between SPCA2 and Orai1 is mediated by both the N- and C-termini of SPCA2, where the N-terminus binds strongly to Orai1 and facilitates the accessibility of the C-terminus to Orai1 and, subsequently, its activation (Fig. 1). Interestingly, even when SPCA1 and SPCA2 N-terminus are highly conserved, although longer in SPCA2, the authors were unable to find an association between SPCA1 and Orai1 [24].

There is only few but strong evidence suggesting that SPCA2 overexpression may be related to some malignancies, including colon [72] and especially breast cancer [24]. SPCA2 has been found to be highly upregulated in the luminal breast cancer molecular subtype as compared to other breast cancer subtypes or non-tumoral breast epithelial cells. The observations in cell lines have been confirmed in primary human breast tumors [24]. The upregulation of SPCA2 in luminal breast cancer cells confers these cells the ability to activate Orai1 channels by a store-independent mechanism providing an additional and specific Ca^{2+} entry pathway for tumorigenicity. In breast cancer cells, SPCA2 interaction with and activation of Orai1 led to a constitutive Ca^{2+} entry and stimulation of Ras–ERK pathway, which, in turn, may trigger uncontrolled proliferation and the development of tumors [24,73] (Fig. 1). In support to this statement, SPCA2 knockdown results in reduced levels of Ca^{2+}, which finally leads to attenuation in proliferation and tumorigenesis in the luminal MCF7 breast cancer line [24,73].

In addition, it has been proposed that high levels of SPCA2 may promote microcalcifications dependent on the Ca^{2+}-ATPase activity in ductal carcinomas, phenomena linked to more aggressive tumors and unfavorable prognosis [74]. The radiographic presence of microcalcifications is commonly found in the breast tumors and is used in mammograms for the diagnosis of breast cancer. While the mechanism underlying the deposition of Ca^{2+} in breast tissue has long remained elusive the study by Dang et al. provide evidence supporting a role for the SPCA isoforms in this process [74]. According to this study both luminal and basal breast cancer subtypes are able to form microcalcifications *in vitro*. Interestingly, these cells exhibit a subtype-specific expression of SPCA isoforms, with higher SPCA1 expression in the basal subtype and SPCA2 upregulation in the luminal breast cancer cells. The functional role of the SPCA isoforms in the formation of microcalcifications was confirmed by gene knockdown and functional expression of the SPCA isoforms. Therefore, these findings suggest that SPCA upregulation in breast cancer cells might enhanced Ca^{2+} loading of the Golgi, thus increasing Ca^{2+} secretion and promoting extracellular calcification [74]. However, while the role of SPCA2 in the store-independent activation of Orai1 has been characterized, the mechanism for Orai1 activation by SPCA1 is unclear. A recent study has revealed that SPCA1 overexpression induces Ca^{2+} influx by an Orai1-dependent and STIM1-independent mechanism elevating the Ca^{2+} concentration in the Golgi and inducing Golgi stress. Impaired SPCA1/Orai1 function has been found to be associated with the Hailey–Hailey disease, a skin disorder caused by SPCA1 loss-of-function [75]. Summarizing, a better understanding of the SPCA–Orai1 pathway might lead to the development of biomarkers or therapies that, eventually, might improve the diagnosis and prognosis of breast cancer.

4. Orai1-K^+ channels complex in cancer development

K^+ channels constitute the largest and most diverse superfamily of ion channels and play a key functional role both in excitable and non-excitable cells. According to the structure and function, K^+ channels can be grouped into five major classes: the voltage-gated (Kv), inwardly rectifying (Kir), Ca^{2+}-activated (K_{Ca}), Na^+-activated (K_{Na}) and tandem

pore domain (K2P) channels. The family of Ca^{2+}-activated K^+ channels includes a number of members with different channel conductances classified into small (SK), intermediate (IK) and big (BK) conductance channels [76]. The small conductance K^+ channel 3 (SK3) is a selective K^+ permeable channel that belongs to Ca^{2+}-activated K^+ channels (KCa) mainly expressed in the central nervous system, regulating neuronal excitability, and in smooth and cardiac muscle, where this channel regulates smooth muscle tone. Like other K^+ channels the structure of SK3 includes four α-subunits, and each of these α-subunits contains six transmembrane domains with the pore-loop formed between the fifth and sixth transmembrane domains. SK3 is a voltage-insensitive channel activated by low concentrations of intracellular Ca^{2+}. Ca^{2+}-dependent activation of SK3 is mediated by the calmodulin (CaM) binding site located in the C-terminal region of each α-subunits [76,77]. Although CaM interacts constitutively with the four CaM binding sites, SK3 activation requires the binding of one Ca^{2+} ion to each CaM [76,78]. Thus, the gating of SK3 channels is regulated by the opening of plasma membrane Ca^{2+}-channels, such as TRPV4 in the late distal tubule and other nephron segments of the kidney [79] and vascular smooth cells [80], and it is also regulated by Orai1 in gallbladder smooth muscle cells [27] and in functional podosomes in microglial cells [81].

In cancer cells, the expression of SK3 is not just confined to those originated from tissues that physiologically express this channel, like gliomas or meduloblastomas. The expression of SK3 in urothelial carcinoma, prostate cancer, breast cancer, melanoma and colon cancer cells has also been reported [26,82,83]. The fact that SK3 is re-expressed in some tumors originated from ectodermal-derived tissues, such as breast cancer, could be explained by the re-expression of an embryonic gene during the dedifferentiation process occurring on cancer development [26,82,83].

In 2006, Potier and coworkers reported for the first time the involvement of SK3 channels in cancer cell migration using the MDA-MB-435s cell line [84]. Plasma membrane hyperpolarization was later identified as a key element for SK3 channel-dependent migration in melanoma cells [26] (Fig. 2). Later on, in 2012, the interaction between SK3 and Orai1 was described [81] as a complex that forms a constitutive Ca^{2+} channel [26], or a STIM1- and store depletion-dependent Ca^{2+} channel [85] depending on the cell studied and the involvement of the TRPC1 channel. The location of both Orai1 and SK3 channels in the lipid raft domains has been reported to be essential for the function of the Orai1–SK3 complex and a delocalization of one of the partners is sufficient to suppress SK3-dependent Ca^{2+} entry and SK3-dependent migration [26,86]. A recent study has reported that Sigma Receptor 1 (SigmaR1), a stress-activated chaperone, may enable the interaction between Orai1 and SK3 channels and their location in lipid nanodomains in breast and colorectal cancer cells. Blockade of SigmaR1 function (by using molecular silencing techniques or ligands like igmesine) reduces SK3 current, Orai1 Ca^{2+} influx and cell migration; on the other hand, high expression of SigmaR1 and Orai1 correlates with a poor prognosis [87].

The coupling between SK3 and Orai1 might be associated to membrane hyperpolarization, which, in turn, results in a stronger electrochemical driving force for Ca^{2+} entry through Orai1, required for cancer cell migration. In colorectal cancer cells, where STIM1 regulates SK3–Orai1 activity, this complex has been implicated in the EGF/PI3K/Akt signaling cascade. EGF and Akt might phosphorylate STIM1 and activate Ca^{2+} entry, which is enhanced by SK3-mediated membrane hyperpolarization and activates Akt. Finally, phosphorylated Akt promotes Rac1/calpain activation and, hence, cancer cell migration [85]. This mechanism is strengthened by high extracellular Ca^{2+} concentrations, and therefore has major relevance on bone metastasis [26]. Moreover, SK3, Orai1 and STIM1 have been detected on the leading edge of migrating microglia, most likely being responsible for the Ca^{2+} influx required for podosome formation, extracellular matrix degradation and cell adhesion. Therefore, SK3 channels may act by enhancing Ca^{2+} entry through Orai1/CRAC channels and are involved in extracellular matrix degradation [81]. The involvement of the SK3–Orai1 complex in native and cancer cell migration deserves further studies to elucidate the precise interaction SK3–Orai1 Ca^{2+} signals with cytoskeleton remodeling.

SK3 channels have been reported to be a target of edelfosine, a glycerophospholipid with antitumor activity that attenuates tumor proliferation and angiogenesis and induces apoptosis [88–90]. The antitumor properties of edelfosine are at least partially attributed on its ability to block SK3 channels and induce plasma membrane depolarization; although this compound shows a variety of side effects [91]. Newly synthesized edelfosine analogues have been found to exhibit antitumor activity and minor side effects [92,93]. These analogues have provided promising results and have been presented as good candidates for cancer therapy, particularly in order to inhibit cancer cell migration and bone metastasis, where the role of SK3 channel activity has been reported to be crucial [92,93].

The interaction of Orai1 with K^+ channels is not limited to SK3 channels. Studies in breast cancer cells have revealed a functional interaction between Orai1 and the voltage-dependent $K_v10.1$ channels that has been reported to be essential for cell migration and collagen-1-promoted cell survival under fetal calf serum starvation [28,94].

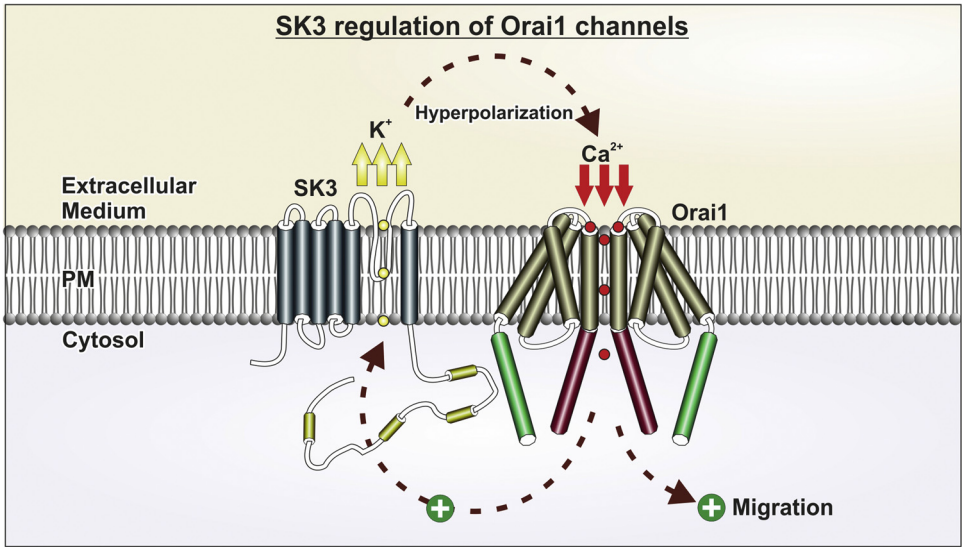

Fig. 2. Constitutive Ca^{2+} entry mediated by the SK3–Orai1 complex. SK3 and Orai1 channels are located in lipid raft domains of the plasma membrane. Ca^{2+} entry *via* Orai1 channels leads to the activation of Ca^{2+}-dependent SK3 K^+ channels, which, in turn, induce membrane hyperpolarization by allowing K^+ efflux. Hyperpolarization enhances the driving force for Ca^{2+} influx through Orai1 and is required for cell migration.

Badaoui and coworkers reported that MCF7 and T-47D cell seeding on a 2D collagen 1 coating significantly enhances $K_v10.1$ and Orai1 channel expression and promotes their co-localization in the plasma membrane. Collagen 1 enhances $K_v10.1$ channel function as well as Ca^{2+} influx in both cell types. Ca^{2+} entry was impaired by silencing of Orai1, $K_v10.1$ or both, thus indicating that $K_v10.1$ sustains collagen 1-evoked Ca^{2+} influx through Orai1 and survival in ER^+ breast cancer cells [28]. Similarly, $K_v10.1$ channels have been reported to support Orai1-mediated Ca^{2+} influx and migration in triple negative MDA-MB-231 cells [94]. A recent study has also reported that SPCA2 is a collaborator of $K_v10.1$ and Orai1 channels in the mediation of pro-survival effects and proliferation induced by collagen 1 in breast cancer cells. SPCA2 enhances membrane expression of $K_v10.1$ and Orai1 and participates in Orai1-mediated Ca^{2+} influx [95].

Altogether, these findings demonstrate a functional relationship between Orai1 and K^+ channels that plays a relevant role in tumorigenesis. These channels might, therefore, represent potential targets for the suppression of cancer cell migration and the development of metastasis and apoptosis resistance.

5. Concluding remarks

Despite the study on Orai1 molecular structure and function has mainly been focused on its role in SOCE, there is a growing body of evidence that supports a role for Orai1 in store-independent Ca^{2+} influx activated by a number of partner proteins of pathophysiological relevance. While some Orai1-mediated SICE mechanisms, *i.e.* arachidonate-mediated Ca^{2+} influx, have been reported in normal as well as in cancer cells, certain pathways appear to be specific or upregulated in tumor cells. Cancer cells are widely heterogeneous, and this variability hinders the development of anti-tumoral strategies but, at the same time, is an opportunity for the development of specific pharmacological tools. The current evidence emphasizes a key role for Orai1 proteins in mediating tumorigenesis. Cancer cells make use of a battery of Orai1-dependent Ca^{2+} entry mechanisms for the development of a number of cancer hallmarks, including cell proliferation, migration, apoptosis resistance or angiogenesis. This scenario makes Orai1 and its molecular partners as attractive therapeutic targets to control tumor growth and metastasis and strongly supports the need to characterize the Orai1-mediated SOCE and SICE pathways in the different cancer subtypes at the molecular level in order to develop specific antitumoral therapies.

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