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Review

Plasma membrane calcium channels in cancer: Alterations and consequences for cell proliferation and migration☆

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ABSTRACT

The study of calcium channels in molecular mechanisms of cancer transformation is still a novel area of research. Several studies, mostly conducted on cancer cell lines, however support the idea that a diversity of plasma membrane channels participates in the remodeling of Ca^{2+} homeostasis, which regulates various cancer hallmarks such as uncontrolled multiplication and increase in migration and invasion abilities. However few is still understood concerning the intracellular signaling cascades mobilized by calcium influx participating to cancer cell behavior. This review intends to gather some of these pathways dependent on plasma membrane calcium channels and described in prostate, breast and lung cancer cell lines. In these cancer cell types, the calcium channels involved in calcium signaling pathways promoting cancer behaviors are mostly non-voltage activated calcium channels and belong to the TRP superfamily (TRPC, TPRPV and TRPM families) and the Orai family. TRP and Orai channels are part of many signaling cascades involving the activation of transmembrane receptors by extracellular ligand from the tumor environment. TRPV can sense changes in the physical and chemical environment of cancer cells and TRPM7 are stretch activated and sensitive to cholesterol. Changes in activation and or expression of plasma-membrane calcium channels affect calcium-dependent signaling processes relevant to tumorigenesis. The studies cited in this review suggest that an increase in plasma membrane calcium channel expression and/or activity sustain an elevated calcium entry (constitutive or under the control of extracellular signals) promoting higher cell proliferation and migration in most cases. A variety of non-voltage-operated calcium channels display change expression and/or activity in a same cancer type and cooperate to the same process relevant to cancer cell behavior, or can be involved in a different sequence of events during the tumorigenesis. This article is part of a Special Issue entitled: Membrane channels and transporters in cancers.

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1. Introduction

Tumorigenesis occurs as a result of mutations driving the transformation of cells and the conferring of cancer-specific hallmarks [1], such as self-sufficiency in growth signals and evasion of apoptosis. Many known mutations lead to the formation of oncogenes, which code for protein kinases [2]. Changes in protein kinase activity that integrate with numerous signaling pathways have major consequences for a variety of processes that drive the cell's fate. Similarly, changes in cytosolic free Ca^{2+} concentration ($[Ca^{2+}]_i$) represent a ubiquitous signaling mechanism, which integrates with other signal-transduction cascades and controls a variety of cellular processes [3]. As for protein kinase, alterations of calcium signaling and homeostasis induce wide ranging consequences, and it is not surprising that some Ca^{2+}-mediated signaling pathways are implicated in tumorigenesis and tumor progression (refs. [4,5]).

The free calcium ion concentration is tightly and precisely controlled in cellular compartments, in order to generate intracellular calcium signals with various amplitudes, as well as different temporal and spatial properties. This precise control is essential for differential modulation, in an individual cell, of various signaling pathways and intracellular Ca^{2+}-regulated proteins involved in specific cellular processes. These include regulation of the cell cycle, proliferation, apoptosis, gene transcription, and cell migration [3]. Since all these functions are relevant to tumorigenesis, the remodeling of intracellular Ca^{2+} homeostasis and of Ca^{2+} signals is thought to be a crucial event in leading to, or maintaining, malignant phenotypes. Indeed, tumor transformation is associated with a major rearrangement of Ca^{2+}-transporting molecules (changes in expression and/or function), which participates with other signaling pathways. This may result in enhanced survival (evasion of apoptosis), excessive proliferation, malignant angiogenesis, cell migration and metastasis (refs. [6,7]). Various modifications of Ca^{2+}-transporting molecules and of proteins regulating calcium homeostasis (the Ca^{2+}-toolkit) have been observed and suggested. Among these are mutations; changes in expression level or in subcellular localization; and regulation by other signaling pathways. These changes can lead to modifications of Ca^{2+} concentration in different cellular compartments and microdomains, as well as changes in intracellular Ca^{2+} signal patterns. This can contribute to a new cell fate by changing the regulation of various calcium-dependent effectors involved in key intracellular signaling pathways (ref. [7]).

2. Plasma membrane calcium channels and transporters

Among the Ca^{2+}-transporting molecules that are affected in various cancer cells, the Ca^{2+} -toolkit at the plasma membrane is essential to control Ca^{2+} entry and extrusion. It may be of great interest as a potential therapeutic target or a prognostic biomarker (refs. [8,9]). Plasma membrane channels support the entry of Ca^{2+} along its concentration gradient across the plasma membrane into the cell. Various calcium channels, such as voltage-gated Ca^{2+} channels (Ca_v family), can be involved in this Ca^{2+} influx. The expression of this family of proteins is a characteristic of "excitable cells," and these channels do require depolarization of the plasma membrane (PM) for activation. However, some of these, such as members of the low voltage-activated (low threshold of activation) Ca_v3 subfamily, are expressed in a number of cancer cell lines, and they modulate proliferation (ref. [9]). Despite Ca_v expression, Ca^{2+} entry in non-excitable cells mostly occurs through non-voltage-gated channels. These include ligand-gated channels (P2X purinergic ionotropic receptor families, for instance); receptor-operated channels (ROC) or secondary messenger-operated channels linked to GPCR activation (SMOC: Orai family and members of TRP (Transient Receptor Potential) superfamily of channels); store-operated channels (SOCE: Orai family and members of TRPC (TRP Canonical) subfamily of channels); and stretch-operated channels (members of TRP superfamily of channels). Numerous studies have shown that one or several of these PM Ca^{2+}-permeable channels are modified in expression and/or activity in different cancer cells, and play a role in most of the pathophysiological processes driving the malignant phenotype (refs. [6,7]). In addition to the PM Ca^{2+} channels, changes in Ca^{2+}-transporters such as PMCA (Plasma Membrane Calcium ATPase) and Na^+/Ca^{2+} exchanger have also been reported to be involved in the Ca^{2+} homeostasis of cancer cells, and to tumorigenesis (refs. [6,7]). In addition to PMCA Ca^{2+}, other intracellular transporters, in particular SERCA, have also been described as playing critical roles in tumor cell fate.

Among PM channels, TRP protein expression is modified during cancer progression, and can represent diagnostic/prognostic markers (ref. [10]). Mammalian TRP proteins assemble as homo- or hetero tetramers and build non-selective Ca^{2+}-permeable cation channels (refs. [11,12]). TRP channels enable cells to sense changes in their local environment, and can be stimulated by a variety of different stimuli. These can be physical (temperature, osmotic pressure, or mechanical stress); or chemical (pH, ROS, pO_2, growth factors and cytokines); and are key elements in the tumor environment. TRP proteins, the expression of which is frequently changed, are members of the TRPC (TRPC1 and 6), TRP vanilloid (TRPV2 and 6), and TRP Melastatin (TRPM7 and 8) subfamilies. Some TRP channels, such as TRPV2, respond to diverse stimuli that include heat, mechanical stress, and growth factors. The activation mechanism of TRPM subfamily channels is equally varied: TRPM8 is activated upon cooling, and is sensitive to intracellular pH, while TRPM7 is regulated by intracellular concentration of Mg^{2+} and by mechanical stimuli. TRPC channels are activated through pathways coupled to the activation of the PhosphoLipase C (PLC), and can support Receptor-Operated Ca^{2+} Entry (ROCE) [13]. Interestingly, TRPC1 and TRPC6 have also been suggested to be activated by PM stretch. Moreover, TRPC1 and TRPC4 have been shown to support relatively non-selective cation currents that contribute to Store-Operated Calcium Entry (SOCE) [13]. SOCE is calcium entry stimulated by depletion of internal Ca^{2+} stores following calcium release. It is dependent upon the ER (Endoplasmic Reticulum) Ca(2+) sensor protein STIM1 (STromal Interaction Molecule 1). STIM1, when localized at the reticulum membrane, senses the Ca^{2+} in the lumina of the endoplasmic reticulum and is stimulated by store depletion. STIM1 activates SOCE through its interaction with Orai1 channels at the PM (ref. [14]). Orai1 is a calcium channel widely expressed in various cell types, and forms the pore of calcium selective channels that mediate SOCE. STIM1 also interacts with TRPC1 [15], and TRPC1-Orai1-STIM1 ternary complex has been described as contributing to functionally distinct SOCE [16].

Numerous examples of Ca^{2+}-toolkit remodeling and Ca^{2+} mishandling are provided by the literature, and some of these changes have been proposed to be significant drivers promoting and maintaining the tumor phenotype. Currently, the Ca^{2+}-permeable channels of the PM represent the more promising candidates for pharmacological therapeutic targets. Modulators of the Ca^{2+} toolkit have been shown to reduce or reverse malignant phenotype in various cancer cell lines (refs. [7,9]). However, the poor selectivity of pharmacological drugs available constitutes a major limitation for clinical use. Moreover, the ubiquitous role of Ca^{2+} signaling may suggest that targeting the PM Ca^{2+} channels will exhibit poor selectivity over cancer cells. In this context, inhibiting or modulating some of the Ca^{2+} channels which are significantly upregulated in cancer cells, and have a restricted tissue distribution, could prevent systemic consequences. The study of calcium homeostasis and the Ca^{2+} toolkit in cancer cells is a rather novel area of research, and most of the data available has been obtained in in vitro cell lines and a few primary human cancer cells. Although the role of the PM Ca^{2+} channels is just beginning to be understood, experimental evidence has suggested involvement in key determinant malignant processes in cellular models from tissues such as breast, prostate, lung and colon, where some of the most common cancers develop.

The present review focuses on the role of the PM Ca^{2+}-channels in regulating proliferation or migration and metastasis in cancer cell lines. Numerous reviews have presented global changes of the Ca^{2+}

toolkit in cancer cells or tumors. We have chosen to focus particularly on studies that provide a clear functional role of PM Ca^{2+}-channels and describe downstream intracellular signaling pathways leading to changes in proliferation or migration in three common cancer types: prostate, breast, and lung.

3. Ca^{2+} and proliferation

It is well-known that cell proliferation is dependent on the cell cycle, which consists of four primary phases: G1, the first gap phase; S phase, in which DNA synthesis occurs; G2, the second gap phase; and M phase, or mitosis, in which the chromosomes and cytoplasmic components are divided between two daughter cells. The transitions between these different phases are tightly controlled, and checkpoints during the cell cycle determine whether the cell proceeds to the next phase [17]. These checkpoints have been shown to be dependent on calcium. Variations in $Ca^{2+}{}_i$ are known to play a pivotal role throughout the cell cycle, during the early phase G1 and at the G1/S and G2/M transitions (ref. [5]): Several studies have established that cell proliferation and division are dependent on extracellular Ca^{2+}, and that increases in basal $Ca^{2+}{}_i$ or a transient increase in Ca^{2+} is involved in cell cycle progression and cell proliferation (refs. [18,19]). During the cell cycle, Ca^{2+} transients have been characterized during G1 and mitosis [20]. Ca^{2+} is required early in G1, as cells re-enter the cell cycle, to promote the activation of AP1 (FOS and JUN) transcription factors, c-AMP-responsive element binding (CREB) protein, and the nuclear factor of activated T-cell (NFAT). Calcium plays a key role through these factors in coordinating expression of cell cycle regulators such as the D-type cyclins, which are required for the activation of cyclin-dependent kinase 4 complexes. The assembly of D-K4 and E-K2 complexes is also dependent on the concentration of $Ca^{2}{}_i$, and this activation controls the phosphorylation and inactivation of retinoblastoma (RB1), which is involved in entry into S phase. The initiation of the centrosomal duplication at the G1/S phase is also dependent on Ca^{2+} and on calmodulin (CaM), CaM kinase II (CaMK) and the centrosomal protein CP110. Calcium/CaM/CaMK pathways were shown to be necessary for cell cycle progression (ref. [18]). CaM was shown to be required at two points, early after mitogenic stimulation and late in G1 near the G1/S boundary [21,22]. The point in late G1 when Ca^{2+}/CaM is required was before the restriction point and pRb phosphorylation [23]. The calcium/calcineurin pathway is also implicated in the regulation of cell cycle checkpoints. Calcineurin, a calcium-dependent phosphatase, also plays a major role in progression through G1 and S phases, and was shown to regulate Cyclins A and E [24], as well as accumulation of cyclin D1 [18]. Calcineurin is also very well-known to activate NFAT, and a demonstrated link with MYC [9,25] regulating cyclins E and E2F provides another connection between calcium-dependent pathways and proliferation.

The calcium/calcineurin/NFAT pathway is one of the major routes that can be activated by calcium entry through plasma membrane calcium channels. For instance, TRPC6 and TRPV6 were both shown to stimulate NFAT-dependent gene transcription in prostate cancer cells [26,9,27]. The use of various calcium channel blockers (against voltage-activated and non-voltage-activated channels) has supported the idea that calcium influx plays a role in cell proliferation. Antiproliferative effects have been demonstrated in various tissues, in response to the blockade of voltage-activated and non-voltage-activated channels. This result was also confirmed by knock-down of calcium channel expression, which strongly inhibited cell proliferation. These observations, as well as variations in channel expression during the cell cycle, suggest that a decrease in calcium channel expression will lead to cell cycle arrest [28]. However, some cancers are characterized by alterations in specific aspects of calcium signaling involved in the proliferative phenotype. For instance, enhanced TRPC3-dependent Ca^{2+} influx leads to increased proliferation in ovarian cancer [29]. Other studies have shown the TRPC1 knock-down induced cell growth arrest by blocking the cell cycle in G0/G1 phase in endothelial progenitor cells [30] or by causing incomplete cytokinesis in gliomas [31].

3.1. Calcium channels, proliferation and prostate cancer (Fig. 1)

In men, prostate cancer (PCa) is one of the most frequent and deadly cancers. The progression of the disease is usually slow or mild in diagnosed patients, but the metastatic form is the second most common cause of mortality [32]. The early stages of this cancer are androgen-dependent, unlike the late stage. Ablation is the first-line treatment, but some patients relapse because of the dissemination and survival properties of the resistant cells. Pharmacological or surgical androgen deprivation therapies are used for treatment of advanced PCa, but alterations in Ca^{2+} homeostasis contribute to PCa cell resistance to androgen deprivation. Alterations in calcium entry pathways through PM calcium channels are also implicated in maintaining cancer cell proliferation.

Changes in expression of TRP channels have been implicated in PCa, including TRPV1, TRPV2, TRPV6, TRPM8, TRPM2, and TRPC6. TRPV6 (TRP vanilloid subfamily) is a highly Ca^{2+}-selective ion channel with a preference for Ca^{2+} over monovalent cations. This property allows TRPV6 to support selective Ca^{2+} influx pathways in non-excitable cells, and these channels have been reported to play a role in PCa. Transcripts of TRPV6 are detectable in PCa, while the expression of TRPV6 mRNA is low or undetectable in benign human prostate tissue [33]. Expression of TRPV6 mRNA is also increased in human PCa cell lines (LNCaP, PC-3) compared to normal and benign epithelial cells (PrEC, BPH1) [34]. TRPV6 is considered to be a strong marker of tumor progression and subsequent invasion, since the expression of TRPV6 mRNA is high in advanced PCa, and significantly correlates with the Gleason >7 grading [35,33]. TRPV6 supports highly calcium-selective currents in prostate cells [36–38]. Some data obtained in human PCa cell lines (LNCaP) suggested that TRPV6 is constitutively open, and mediates calcium entry in these cells without specific activation [27]. *TRPV6* overexpression in LNCaP cells enabled investigators to record a calcium-sensing Ca^{2+} I_{TRPV6} current, which could be distinguished from native I_{SOC} by mechanism of activation, for instance [37]. However, in PCa cells, TRPV6 was shown to contribute to SOCE in addition to TRPC1 and Orai channels, but TRPV6 was not transactivated by STIM1, as SOC was [39]. It was suggested that the increased calcium entry in PCa cells and the contribution of TRPV6 to SOCE involve translocation of the TRPV6 channel to the plasma membrane via the Orai1/TRPC1-mediated Ca^{2+}/Annexin I/S100A11 pathway [39]. TRPV6 was shown to decrease the proliferation rate, as well as cause accumulation of cells in the S-phase of the cell cycle [27]. Treatments with siRNA-TRPV6 also suggest that its role in cell proliferation is affected by calcium-dependent NFAT transcription factor-mediated signaling pathways. Furthermore, such cell cycle markers as cyclin D1, CDK4, and PCNA were detected in tumors induced by TRPV6-overexpressing PC3 cells [39].

Receptor-operated channels or second-messenger-operated channels are also very important mediators of calcium entry in response to extracellular agonist and PLC-pathway activation. Members of the TRPC subfamily are known to constitute ROCs and SMOCs, and TRPC6 protein and mRNA expressions were found to be significantly increased in prostate cancer tissues when compared to benign prostatic hyperplasia (BPH) cases. TRPC6 expression was associated with histological grade and Gleason score increase, and extra-prostatic extension of prostate cancer [40]. Similarly to TRPV6, TRPC6 was described as controlling the proliferation and NFAT pathways. Alpha1-adrenergic receptors (AR) were shown to promote the proliferation of primary human prostate cancer epithelial (hPCE) cells by inducing TRPC6-dependent Ca^{2+} entry and subsequent activation of NFAT. TRPC6 silencing by antisense decreased both hPCE cell proliferation and alpha1-AR-induced calcium entry [26].

In response to these studies, the group of Natalia Prevarskaya has proposed that basal prostate cancer cell proliferation is under the

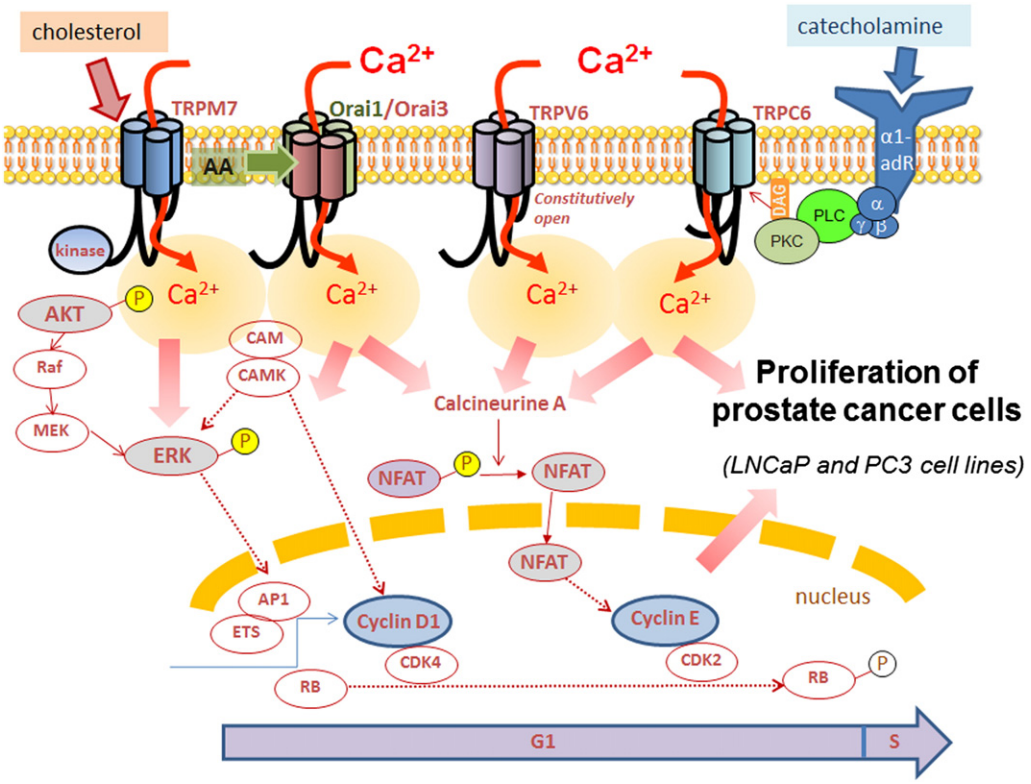

Fig. 1. Implication of plasma membrane calcium channels in cell cycle regulation and proliferation in prostate cancer cell lines. TRPV6-dependent calcium entry and TRPC6-dependent calcium entry in response to catecholamines regulate proliferation through a NFAT pathway. Cell cycle progression is also regulated through Cyclin E, which is known to be under the control of the NFAT pathway. Heteromeres of Orai1 and Orai3 (here postulated as a hexamer of two Orai3 and four Orai1 according to ref [46]) conduct an arachidonic acid-dependent calcium entry. In this hypothetic model, this influx regulates proliferation through NFAT and ERK pathways and cell cycle progression through Cyclin D1, which is known to be under the control of ERK pathway. ERK phosphorylation can be regulated by the calcium-dependent calmodulin–CAMK pathway. TRPM7 was suggested to regulate proliferation under the control of cholesterol and through AKT and ERK pathways. ERK phosphorylation can be regulated by the calcium-dependent calmodulin–CAMK pathway and the AKT–Raf–MEK pathway.

control of TRPV6 supporting a basal calcium entry, and that TRPC6 is involved in the mitogenic effect of catecholamines [9].

Among TRP channels, TRPM7 is distinctive in its own atypical serine/threonine kinase domain, and in its permeability to Ca^{2+} and Mg^{2+}. TRPM7 is expressed in control and prostate cancer cells. It is of interest that an increase in the extracellular Ca^{2+}/Mg^{2+} ratio led to a significant increase in the cell proliferation of PCa cells when compared with control cells [41]. TRPM7 expression was not dependent on the Ca^{2+}/Mg^{2+} ratio per se. However, the same group showed that cholesterol treatment activates TRPM7 channels, thereby increasing cytosolic Ca^{2+} levels. This not only enhances TRPM7 expression, but also promotes cell proliferation in PCa cells [41]. Cholesterol increases Ca^{2+} entry via the TRPM7 channel, which promotes the proliferation of prostate cells by inducing the activation of the AKT and/or the ERK pathways [41]. This may be one of the cellular mechanisms explaining why high circulating cholesterol levels have been shown to increase the risk of overall aggressive PCa [42]. Among the melastatin subfamily, the TRPM8 expression level was found to be elevated in androgen-sensitive cancerous cells compared with normal cells [43,44]. Experiments using LNCaP cells, the TRPM8 antagonist capsazepine, and TRPM8 siRNA indicate that this channel is required for cell survival, but no evidence of effects on cell proliferation has been provided [45].

A recent study has suggested a predominant role of Orai proteins in LNCaP cells [46,46]. Silencing of Orai isoforms substantially reduced LNCaP proliferation and mediated a downregulation of the oncogenic cell-cycle protein cyclin D1, which is involved in G1 phase progression. Silencing of STIM1 had no effect, suggesting a SOCE-independent regulation. Conversely, PCa progression was associated with enhanced Orai3 expression, which favors its heteromerization with Orai1 to form a store-independent channel. Heteromeric association of Orai1/Orai3 was thus proposed to control the proliferation of PCa cells independently of STIM1 and SOCE. These Orai1/Orai3 heteromeric channels support arachidonic acid-mediated Ca^{2+} entry, thereby promoting LNCaP cell proliferation.

Surprisingly, although PCa cells are not an electrically-stimulated type of cell, expression of voltage-operated calcium channels has also been suggested to be involved in the control of cell growth. The L-type calcium channel *CACNA1D* gene expression levels were significantly higher in PCa tissues than in non-cancer tissues, and were highly expressed in androgen-resistant PCa [47]. The study demonstrated that decreasing *CACNA1D* gene expression suppressed androgen-stimulated calcium influx, androgen receptor transactivation, and cell growth in PCa cells. A role for T-type Ca^{2+} channels in proliferation has been also suggested in prostate tumors [48,49]. The small molecule TH1177, which inhibits low-voltage activated T-type Ca^{2+} channels, reduced PCa cell proliferation in vitro by a cytostatic mechanism. However, TH1177 was shown to affect intracellular Ca^{2+} increase after depletion of Ca^{2+} stores by thapsigargin or after ATP stimulation [48]. Moreover, a small proportion of LNCaP cells displayed a weak inward calcium current (LVA T-type properties), and this proportion and the calcium current density are increased during neuroendocrine differentiation [49]. T-type calcium channels participate in a “window” calcium current active at resting membrane potential, and it is proposed that this voltage-dependent calcium channel could participate in the stimulation of mitogenic factor secretion by neuroendocrine prostate cells.

3.2. Calcium channels, proliferation and breast cancer (Fig. 2)

Breast cancer is the most frequent cause of death from cancer in women, worldwide. The most common form is invasive ductal carcinoma, and the aggressiveness of the different cancers has been correlated

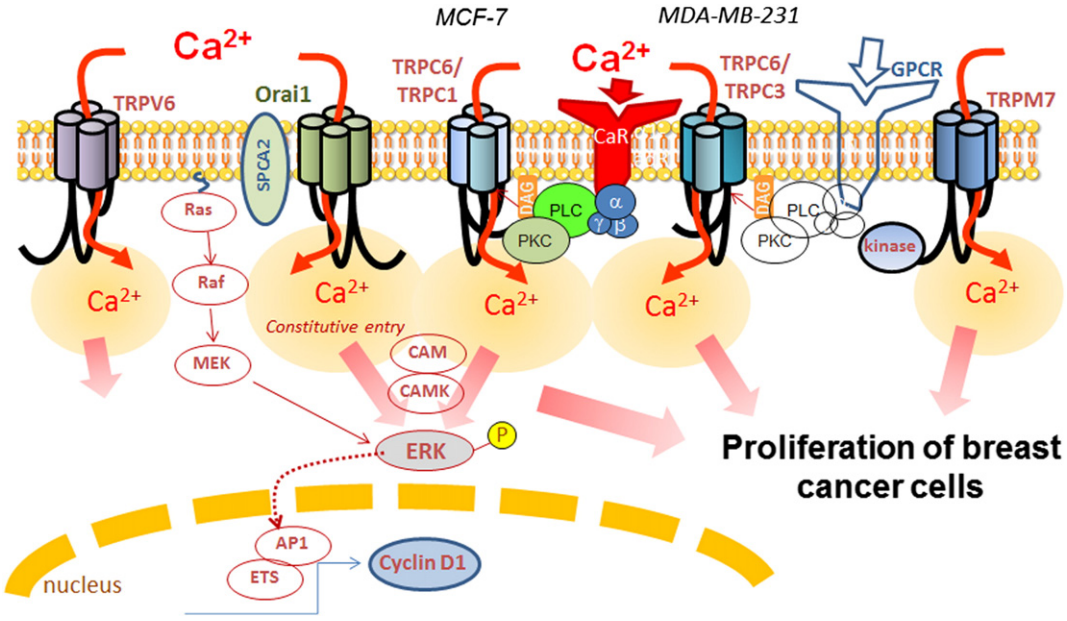

Fig. 2. Implication of plasma membrane calcium channels in cell cycle regulation and proliferation in breast cancer cell lines. Orai1 channels (here represented as the canonical homotetramer) conduct a constitutive calcium entry under the control of SPCA2 membrane proteins. This influx regulates proliferation through ERK pathway and cell cycle progression through Cyclin D1, which is known to be under the control of ERK pathway. ERK phosphorylation can be regulated by the calcium-dependent calmodulin–CAMK pathway. MCF7 cell proliferation can be regulated through this pathway by a calcium entry dependent on TRPC6/TRPC1 tetrameric channels and stimulated by a Calcium-sensing Receptor. In MDA-MB-231 breast cancer cell lines, heteromeric TRPC6-TRPC3 channels were suggested to regulate proliferation through calcium entry. TRPM7 and TRPV6-dependent calcium entry were also suggested to regulate the proliferation of breast cancer cells.

with biomarkers. For example, cancers that have estrogen receptor expression will allow treatment with hormonal therapy, and this is usually associated with a good prognosis. The remodeling of calcium signaling appears to differ between subtypes of breast cancer and can be mediated via various mechanisms leading to different consequences (ref. [50]). TRPC1, TRPC3, TRPC6, TRPM7, TRPM8, and TRPV6 expressions were correlated with breast cancer progression (ref. [51]). As for prostate cancer, various TRP channels, such as TRPV6, TRPC6 and TRPM7, have been implicated in the control of breast cancer cell proliferation.

TRPV6 expression is increased in tumors of the breast and also of the prostate, thyroid, colon and ovary [52,53]. High levels of TRPV6 were reported in a subset of breast cancer biopsies [54,55], which likely belong to the estrogen receptor-negative group [56]. TRPV6 silencing was shown to reduce basal calcium influx and cellular proliferation in T-47D cells, a breast cancer cell line with increased endogenous TRPV6 expression [56]. The percentage of cells in S-phase significantly decreased with TRPV6 knockdown, and TRPV6 silencing caused cells to accumulate in the G1-phase at 24 h. This accumulation in the G1-phase is likely due to the reduction of Ca^{2+} influx, since Ca^{2+} is well-known to promote the G1-phase to S-transition. It is of interest that it has been shown that the tumor suppressor Numb1 interacts with TRPV6, and the resulting complex inhibits TRPV6-dependent calcium entry [57]. In this study, it was suggested that GSK3β, MAP Kinase, and AKT are intracellular signaling pathways involved in the TRPV6-mediated cell proliferation of TRPV6-overexpressing MCF-7 and PC-3 breast cancer cells. The downstream signaling pathway appears to be different from the one proposed in PCa cells.

Different studies have reported significantly-elevated TRPC6 mRNA in breast tumor samples compared with control samples [55,58]. TRPC3 and TRPC6 were found to be in an immunoprecipitable complex. Hyperforin, a specific activator of TRPC6, significantly decreased the growth and viability of the breast cancer cell lines, but had no effect on the non-cancerous breast cell line. Silencing of TRPC6 resulted in a significant reduction in cell growth. TRPC6 siRNA reduced the growth of MDA-MB-231 breast cancer cells but not their viability [58]. These data suggest that TRPC3 and TRPC6 form heteromultimeric channels in the breast cancer epithelial cell line MDA-MB-231, which can be activated in response to agonist-stimulated PIP_2 hydrolysis and regulate cell proliferation. Similarly, a cationic channel in MCF-7 cells was proposed to be constituted as heteromultimers, including both TRPC6 and TRPC1 [59]. It was proposed in this study that the Calcium-sensing Receptor (CaR) activated ERK1/2 via a PLC/PKC-dependent pathway [60] TRPC1 was suggested to be required for the ERK1/2 phosphorylation, fo Ca^{2+} entry and for the CaR-proliferative effect in MCF-7 cells [60]. As for TRPC6, high levels of TRPC1 expression were reported in human breast ductal adenocarcinoma (hBDA) tissue, in comparison to adjacent non-tumor tissue [55]. This correlated with the Scarff-Bloom-Richardson (SBR) grade, Ki67 proliferation index, and tumor size.

Among the TRP melastatin subfamily, TRPM7 levels in human breast cancers indicate that TRPM7 overexpression may be a feature of higher grade and highly proliferative breast cancers [61]. It was proposed that TRPM7 may play a role in the proliferation of MCF-7 breast cancer cells. Moreover, a study reported that TRPM7 and TRPM8 expressions strongly correlated with various tumor aggressiveness markers [55].

Numerous studies have suggested a role of either the calcium Orai channels or the endoplasmic reticulum Ca^{2+} level sensor STIM1 proteins in breast cancer progression (ref. [50]). Orai1 mRNA levels were shown to be elevated in various breast cancer cell lines, such as T-47D, MCF-7 and MDA-MB-468, compared with the non-breast cancer-derived cell lines 184A1 and 184B5. Orai1 up-regulation was shown to be an indicator of the poor-prognosis basal breast cancer subtype, as were higher mRNA levels of STIM1 and lower levels of its related isoform STIM2. Orai1 and STIM1 upregulation suggested that a remodeling of SOCE may be a signature of breast cancers with greater aggressiveness and metastasis [62]. However, a study revealed a mechanism for the activation of Orai1 by SPCA2 that is independent of ER and Golgi Ca^{2+} stores and sensors [63]. This store-independent mode of endogenous Orai1 activation in breast cancer-derived MCF-7 cells underlies constitutive Ca^{2+} signaling, which regulates cell-cycle progression and proliferation. This regulation is mediated by the RAS–ERK pathway. SPCA2 and Orai1-mediated increase of calcium entry was suggested to promote a constitutive activation of RAS signaling, monitored by ERK activation and expression of the downstream protein cyclin D1 [63].

3.3. Calcium channels, proliferation and lung cancer

Lung cancer is the most common and malignant cancer in men, and the second-most in women. The predominant type is non-small cell lung cancer (NSCLC) representing 70–80% of lung cancer, followed by small cell lung cancer (SCLC).

Recent studies have implicated TRPC1, TRPC3, TRPC4, TRPC6, TRPM7, and TRPM8 as playing a role in lung cancer. Among the TRPC subfamily, the expression of TRPC1, TRPC3, TRPC4, and TRPC6 was correlated with differentiation grades in NSCLC [64]. The same study reported that the inhibition of TRPC channels decreased cell mitosis, by using the pore-blocking antibodies T1E3 and T367E3 to inhibit specifically TRPC1 and TRPC3/6 in A549 cells. Blocking of TRPC channels inhibited A549 cell proliferation, while overexpression of TRPC1 and TRPC6 (but not TRPC3 and TPC4) increased proliferation. Another study confirmed that TRPC1 is implicated in the cell proliferation of NSCLC cell lines [65]. Knock-down of TRPC1 with siRNA inhibited cell proliferation and induced G0/G1 cell cycle arrest, resulting in a dramatic decrease in cell growth. TRPC1 was suggested to be the mediator of this regulation through epidermal growth factor receptor (EGFR) phosphorylation and the activation of EGF-induced PI3K/AKT and MAPK downstream signaling pathways [65]. This study proposed that Ca^{2+} entry through TRPC1 constitutes an amplification loop of EGF-dependent cell proliferation: TRPC1-dependent Ca^{2+} entry is triggered by EGFR stimulation, and conversely, it enhances EGFR autophosphorylation and activity. The effect of TRPC1 could be mediated by SOCE, since TRPC1 silencing significantly reduced thapsigargin-induced SOCE in A-549 cells.

A recent study reported that Orai3 also constituted a native SOCE pathway in NSCLC, which controlled cell proliferation and cell cycle progression, likely via the AKT pathway [66]. Orai3 was overexpressed in cancer tissues as compared to non-tumorous tissues, and Orai3 staining was more intense in high-grade tumors. Silencing Orai3 significantly reduced SOCE, inhibited cell proliferation and arrested cells of two NSCLC cell lines in G0/G1 phase. These effects were concomitant with a down-regulation of cyclin D1, cyclin E, CDK4 and CDK2 expressions. Moreover, Orai3 silencing decreased AKT phosphorylation levels. In contrast, overexpression of Orai1 in A-549 cells resulted in the inhibition of EGF-mediated cell proliferation, as well as in attenuation of EGF-mediated store-operated calcium influx [67]. Flow cytometry revealed that the overexpression of Orai1 resulted in G0/G1 cell cycle arrest.

These various studies suggest that SOCE is implicated in the proliferation of lung cancer cell lines, but it is not clear how or by what channels. It has been demonstrated recently that Orai3 is a part of a native store-operated Ca^{2+} entry in estrogen receptor-positive breast cancer cells [68], whereas Orai1 has been described since 2006 as an essential component of the store-operated calcium channels [69]. TRPC1 is also involved in SOCE of lung cancer cell lines [65], and it is proposed by another study that local Ca^{2+} entry via Orai1 regulates plasma membrane recruitment of TRPC1 in HSG cells where Orai1, TRPC1 and STIM1 SOCE are found [70]. However, Orai3 can form store-independent Ca^{2+} channels [71] and heteromeric association of Orai1/Orai3 was proposed to control the proliferation of prostate cancer cells independently of STIM1 and SOCE.

4. Cell migration and metastasis

Cell migration is a process whereby cancerous cells exit the primary tumor, and then disseminate and invade other tissues to develop metastases. In solid cancers, the majority of cells adopt a mesenchymal mode of motility. Recent studies have emphasized the role of certain voltage-independent Ca^{2+} channels, especially subtypes from the Orai and the Transient Receptor Potential (TRP) families, in the process of mesenchymal migration and metastasis formation. Metastasis involves many Ca^{2+}-dependent processes, including cell deformation, invasion, migration and adhesion.

Calcium has been shown to be involved in various steps of migration, including cytoskeleton and focal adhesion (FA) organization, traction force, and directional sensing. The transient increase of this ubiquitous intracellular second messenger triggers specific cellular responses according to its spatial and temporal distribution. A global increase in intracellular calcium concentration usually plays a role in rear detachment by a transient front-to-rear calcium gradient. It involves TRP, voltage-gated calcium channels and the PLC/IP_3R pathway. Transient and local microdomains of calcium have been visualized in different areas of the migrating cells. For example, the so-called "calcium flickers" were restricted at lamellipodia and their occurrence was dependent on the stretch-activated channel TRPM7 [72]. This local increase of calcium does not propagate as a wave through the cell, but its amplitude increases by the local release of IP_3 receptor. This signal plays a role in the organization of FA and actin cytoskeleton by acting on calcium-dependent proteins such as calpain or calmodulin kinase II (caMKII). These, in turn, activate effectors and signaling pathways, such as myosin light chain kinase (MLCK), focal adhesion kinase (FAK), PI3K, and pyk2. It is suggested that TRPM7-induced calcium entry is responsible for the FA disassembling and for the reduction of cell adhesion that promote cell migration. The "calcium flickers" have been also involved in the directionality of chemoattractant-dependent migration. Without such flickering, cells move faster but they decrease their ability to respond to directional cues [72,73].

4.1. Calcium channels, migration and metastasis in prostate cancer (Fig. 3)

The TRPV2 channel is activated in most non-excitable cells by various growth factors or hormone receptors, which promote TRPV2 dynamic translocation from the endosomal compartment to the PM through a phosphatidylinositol-3 kinase (PI3K)-dependent pathway. TRPV2 expression was reported to be higher in samples from patients with metastatic disease than in samples derived from solid primary tumors, which is consistent with a role in tumor cell migration/invasion. In aggressive, castration-resistant cancer, Monet et al. described a high expression level of the activated channel TRPV2 in the metastasis, compared to primary tumor [74]. This observation suggested a role of TRPV2 in migration and invasion. In this study, different in vitro experimental conditions were used to mimic androgen ablation therapy in men, which highlighted an androgen-dependent expression of TRPV2: Androgen deprivation induced the expression of TRPV2, as well as an increase in basal cytosolic calcium and an augmentation of migration. Moreover, the inhibition of TRPV2 decreased the size of the tumor and the expression of many invasion markers. This work suggested that in the castration-resistant stage, de novo TRPV2 induces a constitutive calcium increase which plays a role in the motility of metastatic cells. This supports the idea that TRPV2 could be a target of androgen-independent aggressive PCa [74]. TRPV2 has also been implicated in the migration of PCa cells, independently of androgen. Indeed, lysophospholipids, lysophosphatidylcholine (LPC) and lysophosphatidylinositol (LPI) can activate the PI3K pathway, which induces the PM translocation of TRPV2 and in turn promotes cell migration of PC3 cells [75]. The same physiological effect of TRPV2 has been described in adrenomedullin (AM) activation. Adrenomedullin is a multifactorial regulatory protein involved in different cancerogenesis processes. AM was shown to induce PI3K activation, TRPV2 translocation to the PM, and an increase in cytosolic calcium concentration, which are suggested to promote the migration/invasion of PC3 cells through FAK phosphorylation [76].

It has been suggested that TRPM7 regulates the mobility of PCa cells via cholesterol-dependent calcium entry. High circulating cholesterol levels have been shown to increase the risk of overall aggressive PCa. Cholesterol activates the TRPM7 channel, which increases the basal calcium concentration and stimulates the calcium dependent protein, calpain. Calpain decreases E-Cadherin expression, which may be the link between TRPM7 and migration [41]. TRPM8 is a cold-sensing channel, responding to changes of temperature or the presence of menthol. It

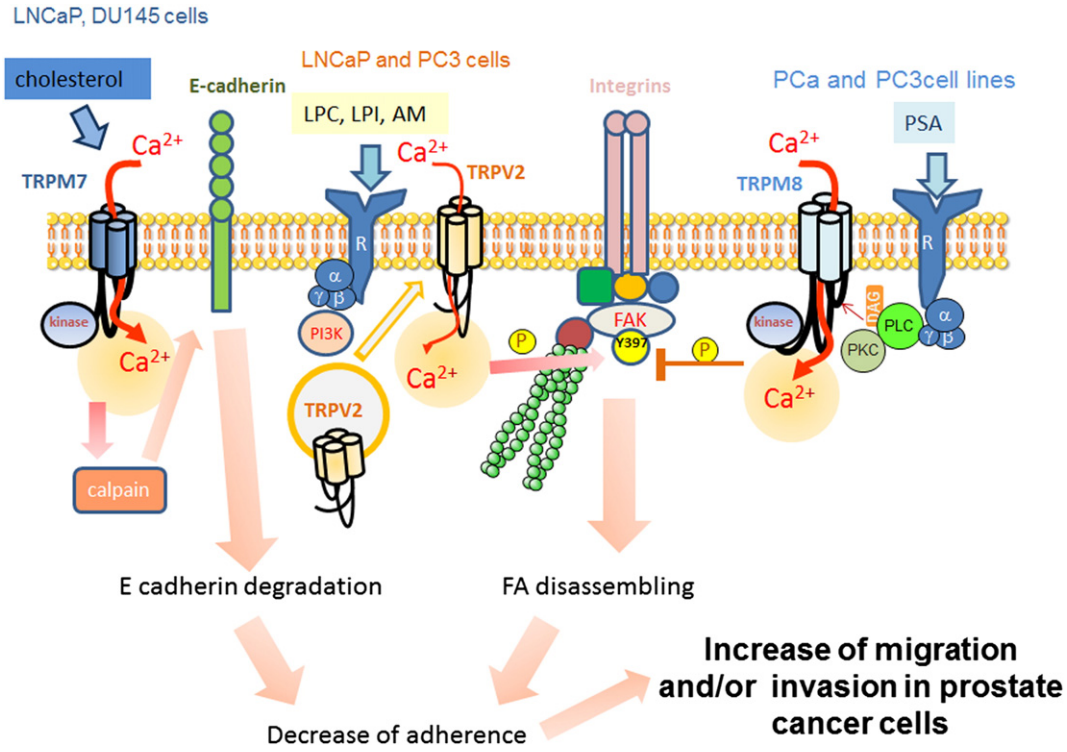

Fig. 3. Plasma membrane channels involved in the intracellular calcium increase link to migration in prostate cancer cells. A large panel of stimuli can activate directly or indirectly specific TRP members (TRPC, TRPV and TRPM). The TRP induced cytosolic calcium increase has various targets that lead to a loose or a decrease of adherence and so a raise in cell mobility. Cholesterol can activate the stretch activated channel TRPM7 that induces the stimulation of the calcium dependent protein: calpain. Calpain dependent proteolysis is involved in E-Cadherin degradation. TRPV2 activation needs the translocation of the channel for submembrane vesicles to the plasma membrane. For the purpose, different stimuli act via G protein associated receptor. The intracellular calcium increase is associated with phosphorylation by FAK inducing FA destabilization. TRPM8 is the only plasma membrane calcium channel link to a protective effect of prostate cancer cells by reducing cell mobility. TRPM8 associated calcium increase inhibits FAK phosphorylation and so plays a role in the maintaining of FA that limits cell migration. Lysophosphatidylcholine (LPC) and lysophosphatidylinositol (LPI), adrenomedullin (AM), focal adhesion kinase (FAK), focal adhesion (FA), prostate specific antigen (PSA).

has been implicated in the regulation of cell migration. TRPM8 can act as a ROC: PSA prostate specific antigen via bradykinin receptor 2. It induces the accumulation of TRPM8 at PM, and the process reduces cell migration though the decrease of FAK phosphorylation. TRPM8 is the only TRP channel described to have a protective role in prostate cancer [77,78].

A recent study involved SOCE and migration of prostate cancer cells through bisphenol A (BPA) incubation. BPA is an endocrine-disrupting compound. It is the principal constituent of reusable water bottles, metal cans and plastic food containers. BPA was found in 95% of samples of adult urine. It is thought to be related to many cancers. BPA regulates the expression of an important component of SOCE: Orai1 (but not STIM1), and also other channels, such as TRPV6 and Ca^{2+}-activated potassium channels BKca and IKca in LNCaP cells. The inhibition of SOCE reduces the migration of androgen-dependent or -independent prostate cells [79].

Taken altogether, Orai and TRP calcium channels are involved in the regulation of the migration of PCA cells. The expression or overexpression of these channels is linked to an increase of mobility (except for TRPM8 in prostate cancer), and can regulate the metastatic stage of carcinogenesis. TRP and Orai channels may be promising targets for cancer therapy, and modulating pathways by blocking PM Ca^{2+} channels presents a promising therapeutic potential to prevent the spread of PCa cells.

4.2. Calcium channels, migration and metastasis in breast cancer (Fig. 4)

Breast cancer-related mortality is associated with the development of metastatic potential of the primary tumor. Recent studies have emphasized that PM calcium channels are critical for breast tumor cell migration, invasion, and metastasis dissemination. The remodeling of the Ca^{2+}-toolkit appears to differ among subtypes of breast cancer, but generally involves Orai and TRP channels, as was previously noted for prostate cancer. Voltage-gated channels have not yet been implicated directly in migration in breast cancer. However, Palmieri et al. propose an epigenetic regulation of CACNA2D3 mRNA: The methylation of CACNA2D3 CpG island may contribute to the metastatic phenotype of breast cancer [80].

Although the expression of SOC, and in particular, of some TRP, was previously correlated to the aggressiveness of breast cancer [55,58], the main SOCE actors Orai1 and STIM1 were recently shown to be directly involved in the migration and invasion of the human invasive cell line MDA-MB-23 [77]. It was reported that knock-down of Orai1-STIM1 by siRNA or inhibition by pharmacological treatment decreased the migration and the invasion in vitro (by Boyden assays) and in vivo (xenograft in mice). Orai1 and STIM1 expressions were directly related to the migration ability of breast cancer cells, because the overexpression of both proteins in non-tumorigenous mammary cells (MCF-10a) with low endogenous Orai1/STIM1 expression did enhance cell migration [77]. This effect was suggested to be linked to the SOCE-dependent intracellular calcium increase, which induced a defect in the turnover of FA. Indeed, the inhibition of Orai1/STIM1 led to an increase of larger FA in the peripheral part of the cell, and this effect was dependent of Ras and Rac pathways [77]. These data are consistent with the role of STIM1- and Orai1-dependent SOCE in the aggressiveness of breast cancer and development of metastasis.

However, Orai1 has also been suggested to be involved in tumorigenesis in a STIM1- and SOCE-independent manner [63]. The analysis of calcium entry in MCF-7 breast cancer cells demonstrated that Orai1 was constitutively activated by the Ca^{2+}-ATPase SPCA2a. In contrast to its well-known Golgi function, SPCA2 co-localized at PM with Orai1. The SPCA2a–Orai1 interaction mediated the activation of the calcium

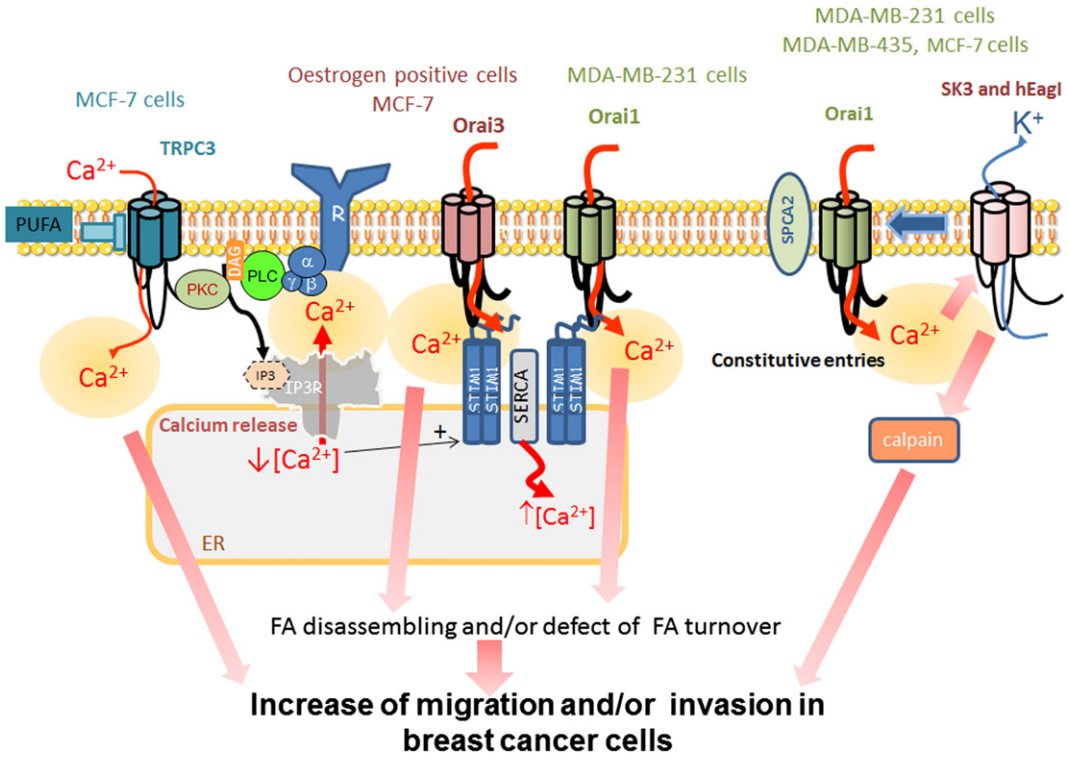

Fig. 4. Plasma membrane channels involved in the intracellular calcium increase link to migration in breast cancer cells. In breast cancer cells, TRPC and Orai family are the main actors of intracellular calcium increase involved in migration or invasion. These channels could be activated by calcium depletion or receptor/PLC pathway leading respectively to SOCE or ROCE but could also be activated by more original pathways. Indeed, like already described, TRPC3 is stimulated by ROCE associated PKC/IP_3 pathways and the ER calcium sensor STIM1 activates the plasma membrane channel: Orai1 and more recently described Orai3 (we have arbitrarily chosen to represent Orai3 as homotetramers like Orai1-based SOC because there is no information about its stoichiometry for its SOC activity). In the other hand, Orai1 mediates also a constitutive cytosolic calcium increase link to K^+ channel membrane depolarization or by the Ca^{2+}-ATPase SPCA2a activation. The entries are independent of intracellular calcium store or of ATPase activity of SPCA2a. Moreover Orai3 is known to be PLA2/acid arachidonic activated channel (ARC) but in breast cancer cells Orai3 can be activated by STIM1 as Orai1 to promote SOCE. All the processes lead to cytosolic calcium increase that stimulates different effectors: calpain or Focal adhesion (FA) proteins. The FA disassembling and defect of turnover promote migration and/or invasion in breast cancer cells. Polyunsaturated fatty acids (PUFAs).

channel independently of calcium store or ATPase activity of SPCA2. Moreover, Feng et al. showed the tumorigenic implication of SPCA2a and Orai1 in breast cancer by in vitro (soft agar colony assays) or in vivo (subcutaneous injection of MCF7 cells) experiments.

Orai3 is well-described as a PLA2/arachidonic acid-activated channel (ARC) but it is also implicated in the regulation of breast cancer in a STIM1-dependent manner. Indeed, Orai3 and STIM1 were suggested to form the main SOCE-induced complex in estrogen-positive MCF7 cells, unlike the coupled Orai1-STIM1 in estrogen-negative cells [68]. In MCF-7, Orai3-dependent SOCE induced the phosphorylation of calcium-dependent effectors ERK and FAK; and knock-down of Orai3 reduced the invasive power of MCF-7 in Boyden and soft agar colony assays. Moreover, in vivo orthotopic injection of shOrai3 MCF-7 cells decreased mammary tumor development in mice [81].

SOCE can also be potentiated by an increase of the driving force of calcium across the plasma membrane. Two K^+ channels, hEag1 and Sk3, were shown to play a role in the migration of breast cancer cells, and hyperpolarization of the membrane due to the activation of hEag1 or Sk3 was suggested to potentiate Orai1-dependent calcium entry and to promote migration [82,83]. Sk3 action was proven to be mediated through an association with Orai1, and the Sk3–Orai1 complex was demonstrated to regulate a constitutive Ca^{2+} entry, calpain activation and cell migration [83].

The stretch-activated channel TRPM7 is a Ca^{2+}/Mg^{2+}-permeable channel, which is necessary for generating "calcium flickers" in lamellipodia of migrating cells [73]. TRPM7 is also involved in migration and metastasis development in breast cancer cells, but this role is due to its kinase activity (MAPK pathway activation and regulation of cells adhesion) in a calcium-independent fashion [84,85].

Other TRP family members can also regulate the migration of breast cancer cells. For instance, TRPV6 was found to be more highly-expressed in invasive parts of tumors, and this observation was correlated in vitro with a TRPV6 role in migration and invasion [55]. Moreover, the activity of TRPC3 has been suggested to be regulated by polyunsaturated fatty acids (PUFAs). This finding could be a new approach to regulate calcium influx in breast cancer cells [86]. Exogenous PUFA inhibited TRPC3-dependent calcium entry evoked by thapsigargin. The migration of MCF-7 cells was reduced by 2-APB, a non-specific SOCE inhibitor [83], but this effect could also be due to the inhibition by 2-APB of store-operated Orai channels.

In breast tumors, the intracellular calcium increase by activation or overexpression of PM channels is associated with an increase in the migration and invasion properties of cancer cells. Recent studies show that Orai/STIM-dependent SOCE is involved in such migration and invasion of breast cancer cells, as is Orai1-dependent constitutive calcium entry, when associated with Sk3 Kca channels. These data suggest that STIM and/or Orai might be good pharmacological targets for metastasis inhibition.

4.3. Calcium channels, migration and lung cancer

Lung cancer has the property of developing early metastasis, and the survival rate is quite low [32]. Invasion, metastasis, and recurrence are common biological characteristics of lung cancer, and they are also the major obstacles hampering therapeutic interventions leading to improved prognosis. Although calcium channels are strongly involved in the proliferation of lung cancer, there is very little data concerning these channels and cell migration. One interesting study suggests a

role for TRPM7 in this pathology. In the NSCLC, TRPM7 is expressed in lung carcinoma tissues. Moreover, mRNA and protein levels are regulated by EGF, an activator of migration in this lung cancer model. The role of TRPM7 in migration was evaluated by siRNA knockdown or by non-specific pharmacological inhibition. As has already been described for breast cancer, the inhibition of TRPM7 induced a decrease of cell migration in basal or EGF-activated conditions [87].

5. Concluding remarks

The study of the role of calcium channels in molecular mechanisms of cancer transformation is still a novel area of research. These studies, while mostly conducted in cancer cell lines, nonetheless support the idea that a diversity of plasma membrane channels participates in the remodeling of Ca^{2+} homeostasis. This then regulates various hallmarks of cancer malignancy, such as uncontrolled multiplication and increased migration and invasion capacity. However, little is yet understood, concerning the intracellular signaling cascades mobilized by calcium influx that participate in cancer cell behavior. The intent of the current review is to bring together some of the calcium channel-dependent pathways described in prostate, breast and lung cancers. In these cancer cell types, the calcium channels involved in calcium signaling pathways that promote tumor activity are primarily non-voltage-activated calcium channels; they belong to the TRP superfamily (TRPC, TPRPV and TRPM families) and the Orai family. TRP and Orai channels are part of many signaling cascades, and TRPV can sense changes in the physical and chemical environments of cancer cells. However, the mechanisms triggering the activation of these channels in cancer cells are poorly understood, depending in some cases upon the stimulation of transmembrane receptors by extracellular ligands from the tumor environment. Some experimental data also suggests that plasma membrane non-voltage-activated calcium channels, such as TRPV6, may be constitutively active in cancer cells. This indicates that these channels are open without the presence of a determined stimulus in the experimental conditions, in the so-called “resting cells”. How, exactly, such non-voltage-activated calcium channels could be open during “resting” conditions in cancer cells is not understood, but may involve macromolecular signaling complexes: Channels and enzymes may cooperate to generate a calcium influx at resting conditions. In breast cancer cells, the cooperation between the Sk3 channel hyperpolarizing the PM and Orai1 channels was proposed to promote a constitutive calcium entry [75]. Other conditions favoring the open configuration may involve phosphorylation of channels by associated kinases or other kinds of post-transductional channel modification by oncogene-activated pathways.

A number of various calcium channels, as well as calcium pumps and transporters, have been linked with cancer cell behaviors and pathophysiological cancer hallmarks. Changes in activation and/or expression of calcium-transporting proteins lead to alteration of the global calcium homeostasis, but also may cause modifications in subcellular calcium microdomains and localized calcium signals. These can affect calcium-dependent signaling processes relevant to tumorigenesis. The studies cited above suggest that an increase in PM calcium channel expression and/or activity can sustain elevated calcium entry (constitutive or under the control of extracellular signals), thus promoting increased cell proliferation and migration. Most of these channels are not specific to cancer cells and are expressed in numerous normal tissues, but some are specifically more active or are overexpressed in cancer cells. A variety of non-voltage-operated calcium channels are changed in the same cancer type. According to the literature, it is likely that several types of channels can contribute to and cooperate in the same tumorigenic cellular process, or can be involved in a different sequence of events during tumorigenesis. However, since these various studies do not support the idea that one channel can be conclusively related to a particular type of cancer, it remains to be determined whether there are specific associations of channels that can be identified.

Targeting these non-voltage-operated channels with pharmacological antagonists could be of interest to regulate uncontrolled tumor cell proliferation, migration, and invasion. In some cancer cells, reduced calcium entry confers resistance to apoptosis by preventing sustained calcium increase in response to pro-apoptotic stimuli [88]. One can also speculate about the use of agonists of non-voltage-operated calcium channels in order to promote in cancer cells a major calcium influx and a sustained elevation of $[Ca^{2+}]_i$. This could lead to the activation of mitochondrial and cytosolic apoptotic pathways [89]. However, selective pharmacological tools against most of these channels remain to be discovered and developed. Since most of these channels are expressed in healthy tissues, a goal would be to couple these chemical agents to a targeting moiety, which will produce an active effector only within the tumor environment.

Transparency document

The Transparency document associated with this article can be found, in the online version.

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