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Ion channels and transporters in cancer. 4. Remodeling of Ca^{2+} signaling in tumorigenesis: role of Ca^{2+} transport

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Lee JM, Davis FM, Roberts-Thomson SJ, Monteith GR. Ion channels and transporters in cancer. 4. Remodeling of Ca^{2+} signaling in tumorigenesis: role of Ca^{2+} transport. *Am J Physiol Cell Physiol* 301: C969–C976, 2011. First published May 18, 2011; doi:10.1152/ajpcell.00136.2011.—The Ca^{2+} signal has major roles in cellular processes important in tumorigenesis, including migration, invasion, proliferation, and apoptotic sensitivity. New evidence has revealed that, aside from altered expression and effects on global cytosolic free Ca^{2+} levels via direct transport of Ca^{2+}, some Ca^{2+} pumps and channels are able to contribute to tumorigenesis via mechanisms that are independent of their ability to transport Ca^{2+} or effect global Ca^{2+} homeostasis in the cytoplasm. Here, we review some of the most recent studies that present evidence of altered Ca^{2+} channel or pump expression in tumorigenesis and discuss the importance and complexity of localized Ca^{2+} signaling in events critical for tumor formation.

ATPases; channels; pumps; local Ca^{2+}, ORAI

THE VERSATILITY and complexity of the Ca^{2+} signal is widely established, with Ca^{2+} ions involved, either directly or indirectly, in almost every aspect of cellular processes (5, 49). Comprising an extensive range of signaling components, including channels, pumps, and exchangers, the Ca^{2+} signaling system is important in the regulation of processes relevant to tumorigenesis, including cell proliferation and apoptosis (5, 49). Research has increasingly focused on the identification of Ca^{2+} transporting proteins, with altered expression in cancer, with several publications reviewing this area (49, 63). The traditional dogma has been that Ca^{2+} pumps and channels contribute to tumorigenesis through alterations in global cytosolic free Ca^{2+} concentration. However, very recent discoveries challenge this traditional emphasis and highlight the importance of localized Ca^{2+} signals from intracellular compartments and subcellular microdomains. These studies also suggest that some Ca^{2+} pumps and channels can promote tumor progression via unique mechanisms, which are independent of Ca^{2+} transporting function. This review aims to provide an insight into the most recent developments and findings relating to aberrant expression of Ca^{2+} transporters in various cancer types and also address current controversial and unexplored areas in the field.

Ca^{2+} Pumps and Channels in Cancer: Recent Progress and Issues

Over the past four years, there has been a significant increase in published work reporting on Ca^{2+} channels and pumps that are associated with cancer. There has also been a significant increase in the types of cancers that are associated with alterations in the expression of specific Ca^{2+} transporters. A summary of important Ca^{2+} transport proteins that are reported to have altered expression or activity in some of the most common cancers is shown in Table 1.

An association between the plasma membrane Ca^{2+}-ATPase (PMCA), a p-type ATPase responsible for the extrusion of Ca^{2+} ions from the cytosol into the extracellular domain, and cancer was established in 1997. SV40 transformed human skin and lung fibroblasts were shown to have reduced levels of PMCA protein (65). Since that time, further work has been published in the area of PMCAs and cancer. An upregulation of the PMCA2 isoform has been shown to occur in some breast cancer cell lines (40), and PMCA also has a potential role in regulating the proliferation of MCF-7 breast cancer cells (41). More recently, work by other laboratories has extended the study of PMCA2 expression to human clinical samples and defined a possible role of PMCA in the acquisition of apoptotic resistance (77). When PMCA2 is overexpressed in T47D breast cancer cells, alterations are seen in the magnitude and recovery of Ca^{2+} transients by an increased capacity to extrude Ca^{2+} from the cytoplasm, significantly reducing apoptosis in response to a Ca^{2+} ionophore (77). PMCA2 overexpression may thus contribute to cancer progression via the acquisition of an apoptotic resistant phenotype. Further linking PMCA2 and tumor characteristics, VanHouton et al. (77) also found an association between PMCA2 levels and tumor grade, nodal metastases, and poor clinical outcome.

As suggested by the early work of Reisner et al. (65) in SV40 transformed cells, PMCA can also contribute to tumorigenesis via reduced expression. PMCA4 mRNA levels are downregulated as an early event in human colon tumorigenesis (2). Correspondingly, when HT-29 colon cancer cells are differentiated with either sodium butyrate or by culturing postconfluence, they have an isoform-specific increase in PMCA4 expression (1, 2). Compromised Ca^{2+} efflux may provide colon cancer cells with a growth advantage through the promotion of proliferative pathways; this remodeling in PMCA expression does not occur to a degree that would sensitize colon cancer cells to apoptotic stimuli (2).

Transient receptor potential (TRP) channels are arguably the most comprehensively studied class of Ca^{2+} signaling proteins in the context of cancer (43, 71). Recent studies such as those linking TRPM8 and TRPV6 channels with prostate cancer (6, 22) have provided new depth into the potential significance of TRP channel expression in cancer. Although the overexpression of TRPV6 in prostate cancer has been established, current research aims to investigate the mechanisms by which TRPV6 overexpression contributes to prostate carcinogenesis. TRPV6-mediated Ca^{2+} influx stimulates activation of the Ca^{2+}-dependent transcription factor nuclear factor of activated T-cells

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Table 1. *Changes in the expression or activity of some Ca^{2+} channels and pumps in selected cancers (patient samples and cell lines) from the top 15 cancer sites for both genders*

Cancer Type and Channel/Pump	Channel or Pump Change in Cancer	References
Prostate cancer		
TRPM8: patient tissue samples	Up*†	24, 62, 72, 75
TRPM8: androgen-independent prostate cancer	Down*	64
TRPV6: patient tissue samples	Up*	22, 58, 85, 92
ORAI1: androgen-independent prostate cancer cell line	Down*†	23
TRPV2: patient tissue samples (androgen-independent prostate cancer)	Up*	48
Breast cancer		
TRPM8: patient tissue samples/cell lines	Up*†	10, 75
TRPV6: patient tissue samples	Up*	92
TRPC6: patient tissue samples/cell lines	Up*†	3, 32
PMCA1: cell lines	Up*	39
PMCA2: cell lines	Up*	40, 77
SPCA2: patient tissue samples/cell lines	Up*	20
ORAI1: cell lines	Up*	47
ORAI3: patient tissue samples/cell lines	Up*	19
Lung cancer		
IP_3R2: patient tissue samples (nonsmall cell)	Up*	34
CACNA2D2: patient tissue samples/cell lines	Down*	44
TRPM8: patient tissue samples	Up*	75
PMCA: SV40 transformed fibroblasts	Up†	65
SERCA2: patient tissue samples	Down*	37
Colon and colorectal cancer		
$Ca_V1.1$ (L-type): patient tissue samples/cell lines (colorectal)	Up*	91
$Ca_V1.2$ (L-type α_{1C}): patient tissue samples/cell lines (colon)	Up*	82
$Ca_V3.1$ (T-type α_{1G}): patient tissue samples/cell lines (colorectal cancer and adenoma)	Down*	74
$Ca_V3.3$ (T-type α_{1I}): patient tissue samples/cell lines (colon carcinomas and adenomas)	Down*	57
TRPM8: patient tissue samples (colorectal adenocarcinoma)	Up*	75
TRPV6: patient tissue samples (colon)	Up*	92
SERCA2: patient tissue samples (colon)	Down*	37
SERCA2: patient tissue samples (colorectal)	Up*	11
SERCA3: patient tissue samples/cell lines	Down†	7, 25
PMCA4: patient tissue samples	Down*	2
Bladder cancer		
TRPV1: patient tissue samples	Down†	38
Melanoma		
TRPM1: patient tissue samples and cell lines	Down*	12, 15
Oral cancer		
PMCA1: squamous cell carcinoma, patient tissue samples/cell lines	Down*†	69
SERCA2: squamous cell carcinoma, patient tissue samples/cell lines	Down*†	17
Thyroid cancer		
TRPV6: patient tissue samples	Up*	92
SERCA2: cell lines	Down *†‡[1]	52
Gastric cancer		
IP_3R3: patient tissue samples (mRNA only)/cell lines	Up*†	70
$Ca_V3.1$ (T-type α_{1G}): patient tissue samples/cell lines	Down*	74
TRPC6: patient tissue samples	Up*†	8
Ovarian cancer		
TRPV6: patient tissue samples	Up*	92
TRPC3: patient tissue samples	Up†	89

Information is from the Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review 1975–2007 from the National Cancer Institute. [1]Microsomal Ca^{2+} ATPase activity. *mRNA; †protein; ‡activity. See text for definitions of abbreviations.

(NFAT) to modulate proliferation and promote resistance to apoptosis in prostate cancer cells (42). Another channel implicated in prostate cancer development is a member of the melastatin subfamily of TRP channels, TRPM8, which is overexpressed in early-stage prostate cancer (90). However, as the disease progresses to a metastatic, androgen-independent stage, TRPM8 expression is downregulated (35, 64). New research has identified a natural agonist for TRPM8 in the prostate. Gkika et al. (28) show that prostate-specific antigen (PSA), a well-known prostate cancer marker, promotes TRPM8 activity via the bradykinin/protein kinase C signaling pathway. Using cell surface biotinylation, they showed that the increased TRPM8 current was due to an increase in functional TRPM8 channels localized to the plasma membrane. Migration assays show that PSA reduces cell motility (28).

Further research into the molecular mechanisms underlying prostate cancer progression shows that TRPV2 has a role. TRPV2 mRNA levels are approximately 12 times greater in patients with late-stage metastatic prostate cancer compared with samples from localized primary solid tumors, suggesting TRPV2 as a potential prognostic marker for this late-stage of disease (48). Overexpression appears to bestow elevated cytosolic Ca^{2+} levels to the cell, which enhances their ability to migrate and invade into adjacent tissue, through direct regulation of key invasion proteases such as the matrix metalloproteinases MMP2 and MMP9 (48). Interestingly, another recent

study reported a progressive decline in TRPV2 levels corresponding to increasing histological grade in human glioma tissue. Small interfering RNA (siRNA) silencing of TRPV2 resulted in increased cell proliferation and resistance to apoptosis via a pathway dependent on extracellular signal-regulated kinase activation (51). Given the association of TRPV2 with prostate cancer and glioma, further studies of TRPV2 in a variety of cancer models are warranted.

Recent work has also extended the association between TRP channels and cancer to other TRP classes and other cancers as exemplified by the marked overexpression of TRPC3 protein in human ovarian cancer samples (89). TRPC3 knockdown using siRNA leads to a decrease in cell proliferation via the induction of G_2/M phase cell cycle arrest, suggesting a functional consequence of the channel's overexpression (89). In support of canonical TRP channels playing an essential role in cell cycle progression, a similar involvement of TRPC6 was recently reported in human glioma cells, where inhibition of TRPC6 activity or expression attenuated intracellular Ca^{2+} influx, also arresting cells at the G_2/M phase and suppressing cell growth (13).

The most rapid acceleration of knowledge in recent years in the field is related to the study of ORAI ion channels in cancer. This is in part due to the identification of STIM proteins and ORAI channels as components of store-operated Ca^{2+} entry in 2005 and 2006, respectively (45, 66, 80). Store-operated Ca^{2+} entry is the predominant manner of Ca^{2+} influx in nonexcitable cells (79). The most widely studied proteins of these classes are STIM1, which functions as an endoplasmic reticulum (ER) Ca^{2+} sensor, and ORAI1, which is an essential component of the channel pore (61, 79). Studies on the role of store-operated Ca^{2+} entry in tumor metastasis were limited until Yang et al. (88) provided evidence for the role of STIM1 and ORAI1 in the migration of MDA-MB-231 breast cancer cells. The study was extended into an animal model, using immunodeficient NOD/SCID mice to confirm a reduction of breast tumor metastasis with STIM1 and ORAI1 knockdown (88).

Subsequent to this work was the finding of McAndrew et al. (47) that ORAI1 levels are significantly elevated (up to 21-fold) in some breast cancer cell lines, relative to normal 184A1 breast cells, and that ORAI1 siRNA-mediated inhibition in MCF-7 and MDA-MB-231 cells attenuates store-operated Ca^{2+} entry and viable cell number. ORAI1 activity may be augmented in some breast cancers via mechanisms distinct from an increase in ORAI1 expression level. An analysis of microarray data from 295 clinical samples of breast cancers showed that tumors defined transcriptionally as basal-like were characterized by high STIM1 and low STIM2 mRNA expression (47). This increase in STIM1 relative to STIM2 was associated with a poorer patient prognosis (47). This study also showed that STIM1 siRNA-mediated inhibition had more pronounced effects on store-operated Ca^{2+} entry than inhibition of STIM2 (47). This work suggests that basal breast cancer cells may have augmented store-operated Ca^{2+} entry.

The association between store-operated Ca^{2+} entry and cancer is now being extended to the less well-studied ORAI channels such as ORAI3. Faouzi et al. (19) report that ORAI3 mRNA is overexpressed in the estrogen receptor-positive breast cancer cell lines MCF-7 and T47D compared with the nontumorigenic MCF-10A breast cell line. ORAI3 mRNA is also increased in some human breast tumors compared with normal breast samples (19). Downregulation of ORAI3 inhibits cancer cell proliferation, contributes to cell cycle arrest at the G_1 phase, and increases apoptotic cell death (19). ORAI3 silencing in the nontumorigenic MCF-10A cells did not change proliferation (19), suggesting that the ORAI3 signaling pathway is a potential therapeutic target in some human breast cancers. Work by Motiani et al. (50) has linked ORAI3 to the store-operated Ca^{2+} entry pathway used in estrogen receptor-positive breast cancer cells and report elevated ORAI3 protein in some estrogen receptor-positive cell lines. Collectively, these results highlight an interesting and diverse role for the store-operated Ca^{2+} pathway components in breast tumorigenesis and attest to the value of further research in this area.

There are limited studies on the role of the principal components of store-operated Ca^{2+} entry in cancers originating from areas outside of the breast. However, interest in other cancer types is an emerging area as reflected in recent work linking ORAI1 to prostate cancer (23). ORAI1 is downregulated during the transition to an androgen-independent phenotype in prostate cancer cells. ORAI1 inhibition in LNCaP cells results in resistance to apoptosis mediated by the sarco-endoplasmic reticulum Ca^{2+}-ATPase inhibitor thapsigargin (23). Furthermore, downregulation of ORAI1 in LNCaP cells protects the cells from chemotherapy-induced apoptosis, using cisplatin and oxaliplatin, two clinically used agents (23). Hence, advanced prostate cancers may acquire resistance to treatment in part due to ORAI1 downregulation. These results reflect the importance of the ORAI/STIM proteins and the store-operated Ca^{2+} signaling pathway in the pathogenesis of cancers and will provoke further research in this field.

Ca^{2+} Transporters and Tumorigenesis: New Mechanisms and New Complexities

The majority of studies in the context of Ca^{2+} transport in cancer have of course focused on exploring the relationship between how alterations in the expression of a Ca^{2+} channel or pump mediate their effects via the direct movement of Ca^{2+} ions through the pore of the channel or pump. However, recent studies in cell lines of both tumorigenic and nontumorigenic origin offer alternative mechanisms. Tumorigenic processes, in some cases, may be promoted via unique mechanisms that are independent of the Ca^{2+} transporting function of the protein or effects on global cytosolic free Ca^{2+}.

The contribution of the secretory pathway Ca^{2+} ATPases (SPCAs) in the context of cancer was largely unexplored until recent work by Feng et al. (20) on SPCA2. SPCA2 is a Golgi-localized p-type Ca^{2+}-ATPase first characterized in 2005 (78, 86). SPCA2 mRNA levels are upregulated in luminal-like breast cancer cell lines (20). The consequence of SPCA2 upregulation is an increase in cell proliferation and tumorigenicity (as assessed by growth on soft agar). Detailed examination into the mechanisms responsible for the effect revealed the ability of SPCA2 to localize to the plasma membrane and elicit constitutive Ca^{2+} influx through direct interaction of its NH_2-terminus with ORAI1 (20). The separation of the ORAI1 activation function from the ion transporting ability of SPCA2 was demonstrated by the ability of ion transport-deficient mutants to activate Ca^{2+} influx, NFAT signaling, and proliferation. This study provides an example of how a Ca^{2+} pump can augment cancer processes via a mechanism distinct

from its primary Ca^{2+} transport function. Physiologically, such a mechanism may be important in processes requiring sustained Ca^{2+} secretion such as lactation, where SPCA2 expression is increased (18).

The complexity of ORAI channel regulation is further highlighted by the ability of STIM2 to activate ORAI1 in a store-independent manner (30). STIM2 has now been reported to exist in distinct functional forms: the widely investigated STIM2 and another population, referred to as pre-STIM2, that is able to escape ER targeting (30). Immunolocalization revealed that cytosolic pre-STIM2 localizes to the plasma membrane, where it interacts with ORAI1, increasing basal Ca^{2+} concentration in a manner that is independent of ER Ca^{2+} store depletion (30). The increase in basal Ca^{2+} concentration by pre-STIM2 results in the induction of NFAT and nuclear factor-κB (NF-κB)-mediated gene transcription (30). Further to this, a third population, which is actually a fragment of the STIM2 signal peptide, upon its release from the ER membrane into the cytoplasm, becomes a regulator of gene transcription in a Ca^{2+} independent fashion (30). Together, these findings support the repositioning of paralogs in protein families into subcellular compartments as an emerging method for the functional diversification of replicated genes (30). Given the role of SPCA2 regulation of ORAI1 in breast cancer, assessment of pre-STIM2 in cancers, including those aside from the breast would now seem a priority. Figure 1 is a schematic representation that summarizes regulators of ORAI1 channels and activation associated with tumorigenesis as described in this review.

SPCA2, which as discussed above, activates ORAI1, is not the only example of a Ca^{2+} transporter with dual functionality. In neuronal cells, the voltage-gated channel $Ca_V1.2$ can produce a COOH-terminal fragment of $Ca_V1.2$ known as Ca^{2+} channel-associated transcriptional regulator (CCAT) (29). CCAT translocates into the nucleus, binds to nuclear proteins such as p54(nrb)/NonO, and regulates the expression of genes critical for neuronal signaling (29). The potential significance of such mechanisms in cancer is still to be explored.

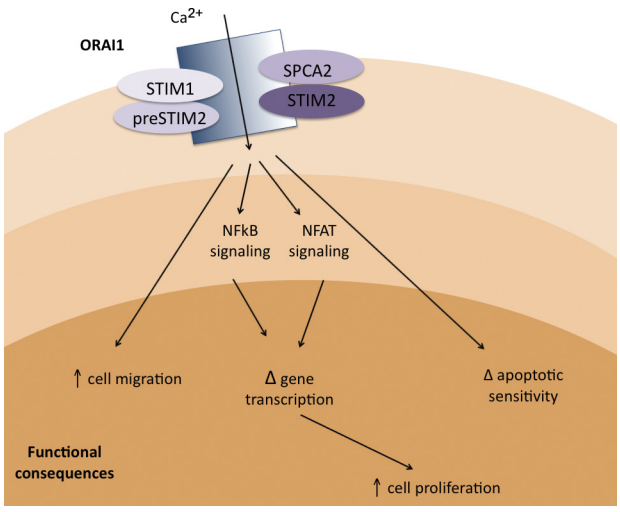

Fig. 1. ORAI1 and cancer. Schematic representation of some regulators of ORAI1 channel activity leading to increased activity of transcription factors such as nuclear factor of activated T-cells (NFAT) and nuclear factor κB (NFκB) and the functional consequences in relation to the development of cancer. Note that this figure is not intended to convey information currently known about the stoichiometry of ORAI1 and its regulators. SPCA, secretory pathway Ca^{2+}-ATPase.

Another recent study by Wang et al. (83) provides further insight into mechanisms by which Ca^{2+} channels may be regulated, suggesting a crucial link between receptor-induced Ca^{2+} store depletion and the control of voltage-activated signals. This group showed that STIM1 activation by store depletion not only leads to the activation of ORAI channels but also attenuates the activity of $Ca_V1.2$ (83). Although the action of STIM1 on $Ca_V1.2$ is independent of ORAI channels, its effects on both of these Ca^{2+} channels are spatially and functionally connected. ORAI channels trap STIM1 in puncta and cause STIM1 to become closely associated with $Ca_V1.2$ channels (83). One could postulate that cancer cells could have deregulation of these complex channel regulation mechanisms.

The arachidonic acid pathway has been implicated as a key inflammatory pathway involved in the cellular signaling contributing to prostate carcinogenesis (56, 76). Arachidonic acid is an inhibitor of TRPM8, a channel overexpressed in androgen-dependent prostate cancer (75, 90). However, the physiological pathways and surface receptors mediating the effect of arachidonic acid on cancer progression remain largely uninvestigated. Bavencoffe et al. (4) have recently reported on the role of arachidonic acid release in the complex regulation of TRPM8 through the M3-type muscarinic acetylecholine receptor-coupled signaling cascade. Their results showed that the application of a nonselective muscarinic agonist suppressed the activity of TRPM8 channels expressed in HEK-293 cells via stimulation of cytosolic phospholipase A2 (cPLA2) and subsequent generation of arachidonic acid. Further research into other surface receptors as regulators of ion channel activity in cancer cells is now required.

Localized Ca^{2+} Signaling

Changes in global cytosolic Ca^{2+} homeostasis through alterations in Ca^{2+} transporter expression or activity has been the focus of researchers characterizing changes in Ca^{2+} signaling in cancer cells (49). Spatially restricted Ca^{2+} signaling within specific cellular compartments or discrete cytosolic domains provides an additional layer of complexity in the regulation of cellular processes important in tumorigenesis; however, this has not yet been extensively assessed in the context of cancer.

Compartmental Ca^{2+}

Ca^{2+} gradients, such as those maintained by the ER, mitochondria, nucleus, and the Golgi help confer versatility to the Ca^{2+} signal, enabling the control of many cellular processes within a single cell (5). An example of the deregulation of Ca^{2+} stores that may occur in cancer is seen in the regulation of ER Ca^{2+} homeostasis by the anti-apoptotic protein BCL2. Ca^{2+} transfer from the ER to the mitochondria, if sufficient in magnitude, leads to the activation of cell death pathways (59). Many studies have now established a role for BCL2 in the inhibition of Ca^{2+} transfer between these often closely apposed organelles (9, 33, 59). A reduction in the luminal ER free Ca^{2+} level ($[Ca^{2+}]_{ER}$), inhibition of Ca^{2+} release from the ER, and inhibition of Ca^{2+} accumulation by mitochondria are all possible mechanisms for the anti-apoptotic effects of BCL2 (14, 33) and are a further link between Ca^{2+} signaling and processes important in cancer. A recent study by Giorgi et al. (27)

identified a role for the promyelocytic leukemia (Pml) protein in ER-mitochondrial Ca^{2+} transfer. Pml is present at ER and ER-mitochondrial contact sites. Studies comparing $Pml^{+/+}$ and $Pml^{-/-}$ mouse embryonic fibroblasts showed that ER-localized Pml is associated with a higher $[Ca^{2+}]_{ER}$ and a larger Ca^{2+} transient in response to apoptotic stimuli. Loss of functional Pml on the ER [as reported in some cancer cells (27)], results in an impairment of Ca^{2+} transfer between the ER and mitochondria and the evasion of Ca^{2+}-mediated cellular apoptosis (27). Hence, therapeutic modulation of targets that regulate $[Ca^{2+}]_{ER}$ and/or ER-mitochondrial Ca^{2+} transfer may be able to augment apoptosis in cancer cells without disrupting global Ca^{2+} homeostasis.

Nuclear Ca^{2+} signaling has been the subject of debate since the first reports of differential Ca^{2+} signaling in the nucleus (26). The notion of a nuclear-cytoplasmic Ca^{2+} gradient has obvious implications for the regulation of gene transcription during tumorigenesis. One possible mechanism for a differential Ca^{2+} concentration between the cytosol and the nucleus may be buffering of Ca^{2+} by perinuclear mitochondria (26). Careful studies in cancer cells are required before the potential impact of this phenomenon on aberrant gene transcription in cancer cells and tumor progression can be fully understood.

Posttranslational protein modification and the trafficking of secreted proteins is the responsibility of the Golgi, which maintains a relatively high luminal Ca^{2+} concentration compared with the cytosol (60). This Ca^{2+} gradient appears to be predominately mediated via SPCAs. Recent studies assessing the potential significance of SPCA1 upregulation in the basal breast cancer subtype has shown that the silencing of SPCA1 inhibits the processing of the insulin-like growth factor receptor-1 (31). This change occurs without an impact on general cytosolic free Ca^{2+} homeostasis (e.g., changes in $[Ca^{2+}]_{CYT}$ recovery after stimulation). Hence, some Ca^{2+} transporters may contribute to tumor progression through alterations in Golgi luminal Ca^{2+}. Rather than altering cytosolic Ca^{2+} dynamics, SPCA1 may contribute to cancer pathways by altering the activity of Ca^{2+}-regulated enzymes that are responsible for the posttranslational modification of proteins important in cell proliferation, apoptosis, and differentiation (31).

Spatial Heterogeneity in Cytosolic Ca^{2+} Signaling

The importance of localized Ca^{2+} signaling during excitation-transcription coupling is increasingly investigated in neurons and during the phenotypic conversion of vascular smooth muscle cells (46, 81). Ma et al. (46) demonstrated a role for local Ca^{2+}/calmodulin (CaM) and calmodulin-dependent protein kinase II (CaMKII) in decoding Ca^{2+} signaling via L-type voltage-gated channels in sympathetic neurons. The ability of CaM to act as both a local and global Ca^{2+} sensor, via its COOH- and NH_2-terminal lobes, respectively, highlights the importance of this protein in integrating the spatiality of the Ca^{2+} signal (73). CaM and CaMKII are deregulated in several cancers including thyroid and prostate cancers (67, 68) and the ability of localized Ca^{2+} signaling to regulate these proteins highlights the need for this aspect of their regulation to be further explored in tumorigenesis. Localized Ca^{2+} events, defined as Ca^{2+} "flickers," are also an important regulator of migration in human embryonic lung fibroblasts exposed to a growth-factor gradient (84) and are another example of a pathway that requires further assessment in cancer cells.

Regulation of gene transcription via NFAT is a defining feature of local store-operated Ca^{2+} entry currents (21), which as discussed previously in this review, is a Ca^{2+} influx pathway increasingly linked to cancer. The NFAT family of transcription factors regulates many cancer-related processes including cellular differentiation, migration, and angiogenesis. Kar et al. (36) recently demonstrated that thapsigargin-induced store-operated Ca^{2+} entry induces NFAT1 nuclear translocation. Through a series of elegant experiments, this pathway was shown to be dependent on the local Ca^{2+} concentration near the Ca^{2+} channel pore. EGTA-AM, a cytosolic Ca^{2+} chelator with a slow Ca^{2+} buffering on-rate, significantly reduced the $[Ca^{2+}]_{CYT}$ response; however, EGTA-AM failed to block NFAT translocation to the nucleus, indicative of a dependence on localized Ca^{2+} signaling. Overexpression and activation of

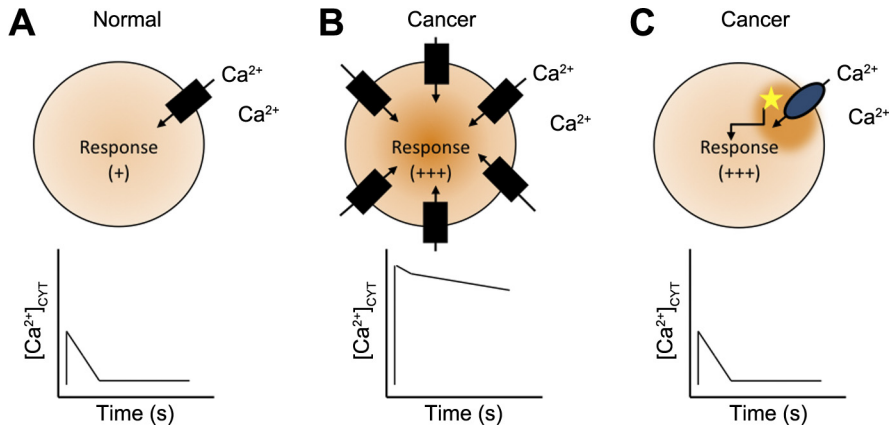

Fig. 2. Contrasting mechanisms for Ca^{2+} transporters in cancer. Ca^{2+} transporters may regulate processes important in tumorigenesis via two broadly distinct signaling mechanisms. Traditionally studies examining the importance of specific transporters in cancer have assessed gene and/or protein expression of these transporters in normal (*A*) versus cancer cells (*B*). Targets identified as having altered expression in cancer (depicted here as an increase in expression) lead to changes in the global cytosolic Ca^{2+} ($[Ca^{2+}]_{CYT}$) profile and augment processes important in tumorigenesis, such as cell proliferation and migration. Although expressed in similar levels to normal cells, Ca^{2+} transporters that act via localized signaling (*C*) may also have major roles in tumorigenesis due to areas of privileged Ca^{2+} signaling activating downstream signaling events. This highlights the importance of an integrated approach to cancer research, utilizing studies assessing the functional role of Ca^{2+} transporters in cancer in addition to the assessment of changes in expression and global cytosolic Ca^{2+} responses.

TRPC3, which produces a similar Ca^{2+} transient to store-operated Ca^{2+} entry, did not induce NFAT translocation (36). Collectively, these results implicate a mechanism whereby the spatial Ca^{2+} concentration gradient in the cytosolic microdomain adjacent to Ca^{2+} channels, such as ORAI1, are important in gene transcription. The recently identified associations with ORAI channels and some cancers provide new impetus to explore this phenomenon in cancer cells.

The link between Ca^{2+} transporters and cancer may be through specific plasma membrane domains such as plasmalemmal lipid rafts and caveolae (54). Caveolae are membranous invaginations that serve as signaling complexes via the clustering of related signaling proteins into discrete microdomains (55). Upon ER Ca^{2+} store depletion, the fraction of the Ca^{2+} channel TRPC1 and the ORAI1 channel activator STIM1 localized to the lipid raft domain increases (53). Several studies have demonstrated an interaction between ORAI1 and caveolin-1 (54), and when combined with studies showing that pharmacological disruption of lipid rafts impairs store-operated Ca^{2+} entry (53), provide compelling evidence for the importance of plasma membrane microdomains in this type of Ca^{2+} influx. This relationship has significant implications in cancer, as the caveolae coat protein caveolin-1 is linked to processes important in cancer metastasis (87) and is enriched in clinical breast cancer samples associated with a poor prognosis (16).

One important implication of localized Ca^{2+} signaling may be a divergence between studies investigating the expression of Ca^{2+} transporters in cancer and those assessing function. Proteins with a relatively low endogenous expression may still wield significant responses in cells due to regions of privileged Ca^{2+} signaling in the vicinity of downstream targets, and thus should not be disregarded as having a role in tumorigenesis (Fig. 2). Conversely, models founded on heterologous expression of proteins that signal via localized Ca^{2+} may be misleading. Forced expression of these proteins may skew the ratio between the protein of interest and its natural downstream signaling partners. Although these studies may provide valuable information for research, they should not be interpreted in isolation, rather in conjunction with studies assessing the functional role of these proteins in physiology and pathophysiology.

Conclusion

In summary, this review has focused on very recent discoveries of changes in the expression and/or activity of important Ca^{2+} transporters in cancer cells, such as the overexpression of TRPC3 in ovarian cancer and ORAI-mediated Ca^{2+} influx in some breast cancer cells. We have also described unusual mechanisms by which some Ca^{2+} transporters contribute to tumorigenesis in a manner distinct from their primary transporting function or global cytosolic Ca^{2+} levels. Over the next five years, we will see current advanced approaches to the study of Ca^{2+} signaling being used to define the mechanisms by which Ca^{2+} transporters contribute to tumorigenesis.

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DISCLOSURES

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