Calcium channels and pumps in cancer: changes and consequences

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SUMMARY

Increases in intracellular free Ca^{2+} play a major role in many cellular processes. The deregulation of Ca^{2+} signaling is a feature of a variety of diseases and modulators of Ca^{2+} signaling are used to treat conditions as diverse as hypertension to pain. The Ca^{2+} signal also plays a role in processes important in cancer such as proliferation and migration. Many studies in cancer have identified alterations in the expression of proteins involved in the movement of Ca^{2+} across the plasma membrane and sub-cellular organelles. In some cases these Ca^{2+} channels or pumps are potential therapeutic targets for specific cancer subtypes or correlate with prognosis.

Our understanding of calcium signaling and its intersection with specific processes important in tumor progression is only recent. We now appreciate that altered expression of specific Ca^{2+} channels and pumps is a characterizing feature of some cancers. By comparison, the link between calcium signaling and other conditions such as cardiovascular and neurological diseases was made many years ago. The direct link between Ca^{2+} and processes linked to a specific pathology, such as vascular tone and neurotoxicity, meant that these conditions attracted the initial focus of researchers devoted to defining the role of Ca^{2+} in disease.

In their seminal review "The hallmarks of cancer" Hanahan and Weinberg (1) described six acquired characteristics of cancers: the ability to evade apoptosis, self-sufficiency in growth signaling, insensitivity to anti-growth signals, the capacity to invade and metastasize, "limitless" replication potential and the promotion of angiogenesis. Calcium signaling is linked either directly or indirectly to each of these processes and this has been reviewed elsewhere (2-6). A remodeling of calcium homeostasis can occur in cancer cells. Although alterations in Ca^{2+} signaling may not be a requirement for the initiation of cancer, the consequences of altered calcium transport in cancer cells may be significant and contribute to tumor progression. Characterizing such changes may help to identify new therapeutic targets. In this review we will discuss how remodeling of Ca^{2+} signaling is a feature of some cancers and provide examples of how this remodeling is often achieved through the differential expression of specific Ca^{2+} pumps and channels. Examples of this remodeling are discussed, particularly those that illustrate the complexities of expression changes and their contribution to tumor progression.

Ca^{2+} transport in cancer cells

Cancer cells use the same calcium channels, pumps and exchangers as non-malignant cells. However, there are often key alterations in calcium channels and pumps in cancer cells. Such changes in cancer cells may include: the expression of calcium channels or pumps (or their specific isoforms) not normally present in non-malignant cells of the same cell type, pronounced changes in the level of expression (as outlined in Table 1), altered cellular localization, altered activity through changes in

post-translational modification, gene mutations and changes in activity or expression associated with specific cancer-relevant processes (e.g. migration). These changes are often reflected in alterations in Ca^{2+} flux across the plasma membrane or across intracellular organelles.

Ca^{2+} influx in cancer

The influx of calcium across the plasma membrane into the cell is a key trigger or regulator of cellular process relevant to tumor progression including proliferation, migration and apoptosis. Ca^{2+} permeable ion channels of almost every class have now been associated with aspects of tumor progression. This review will particularly focus on transient receptor potential (TRP) channels and ORAI-mediated store-operated Ca^{2+} influx as examples of Ca^{2+} influx pathways altered in some cancers.

1. TRP channels

TRP ion channels consist of six subfamilies, with most members permeable to Ca^{2+}, many of which have a role in distinguishing sensations including pain, temperature, taste and pressure (7). This family is arguably the most studied ion channel class in cancer. The key early work on calcium signaling in cancer was focused on cancers of the prostate gland and more specifically the calcium permeable ion channel TRPM8 (8). Although now predominately studied in the context of its role as a cold receptor (9,10), TRPM8 was first identified by its overexpression in some prostate cancers (8). Early work by Zhang and Barritt (11) demonstrated that both the silencing of TRPM8 and menthol-mediated activation of TRPM8 reduced the viability of LNCaP prostate cancer cells. That both activators and inhibitors are proposed as potential therapeutic agents for prostate cancer cells that overexpress TRPM8 is reflective of the duality of the calcium signal (12), whereby Ca^{2+} is both a key regulator of proliferation and in the case of Ca^{2+} overload an initiator of cell death. The ability of TRPM8 activation by prostate-specific antigen to inhibit the migration of PC3 prostate cancer cells now extends the applicability of channel activators as therapeutics beyond just inducers of cancer cell death (13). Further detailed work on TRPM8 in prostate cancer shows androgen-mediated increases in TRPM8 in LNCaP prostate cancer cells (11,14). This finding provides one of the first examples of hormone-mediated changes in the expression of a calcium permeable ion channel in a cancer cell line. As discussed later in this review, this has now been seen with other calcium channels and pumps in breast cancers.

The contribution of TRPM8 to cancer progression, as we will see for other Ca^{2+} channels and pumps, may not always involve its classic role (in this case as a plasmalemmal ion channel). As opposed to the usual plasma membrane localization, endoplasmic reticulum localization of TRPM8 is observed in some prostate cancer cells (11,15) with the consequence being reduced levels of endoplasmic reticulum Ca^{2+} and increased resistance to apoptosis (15). Aside from prostate cancer, overexpression of TRPM8 is also associated with other cancer types including melanoma and cancers of the pancreas, breast, colon and lung (see Table 1). However, the utility of TRPM8 as a target for cancer therapy might be limited and require knowledge of the individual tumor expression of the channel. For example, TRPM8 expression actually appears to reduce as prostate cancer cells transition to androgen independence and increased aggressiveness (16,17).

TRPV6 is another TRP channel linked to prostate cancer. TRPV6 levels correlate with tumor progression and have been proposed as a predictor of invasiveness (18,19). TRPV6 is highly Ca^{2+} selective and is constitutively active (20). When TRPV6 expression is silenced in LNCaP prostate cancer cells there is inhibition of Ca^{2+} influx and consequently reduced activation of NFAT. Crucially this illustrates the importance of calcium dependent transcription pathways as a mechanism for tumor promotion (19).

Like TRPM8, alterations in TRPV6 expression are not confined to cancers of the prostate, with increased expression levels reported in thyroid, colon, ovarian and breast cancers (Table 1). In breast cancers the expression of TRPV6 varies widely between tumors (21). The consequences of TRPV6 overexpression in tumors may relate to effects on cancer cell survival, as TRPV6 silencing in T47D breast cancer cells reduces cell viability (21). Further studies are needed to address the mechanisms leading to TRPV6 overexpression in cancers and the association between TRPV6 levels and breast cancer

prognosis. Analogous to the androgen dependence of TRPM8 expression in LNCaP prostate cancer cells, TRPV6 levels also appear to be hormonally regulated with estradiol increasing TRPV6 mRNA in T47D breast cancer cells (21).

Other examples of TRP channels that are overexpressed in multiple cancer types include TRPC3 and TRPC6. TRPC3 is elevated in some breast (22) and ovarian epithelial tumors, and its silencing reduces ovarian cancer cell line proliferation *in vitro* and tumor formation *in vivo* (23). TRPC6 is elevated in cancers of the breast, liver, stomach and esophageous, and in gliomas (22,24,25), and its silencing reduces the proliferation of some esophageal and breast cancer cell lines and glioma cell lines (22,24,25). For esophageal and glioma cell lines these effects are due to G2/M cell cycle arrest (24,25).

The importance of some TRP channels in tumor progression appears to extend beyond the primary tumor. Fiorio Pla et al. (26) showed that migrating endothelial cells have a greater $[Ca^{2+}]_{CYT}$ response to the TRPV4 activator 4αPDD than non-migrating cells. Furthermore they showed increased expression of TRPV4 in endothelial cells derived from breast cancers compared to those derived from normal tissue, implicating TRPV4 as a possible key component in angiogenesis associated with breast cancers. Other Ca^{2+} channels have also been associated with angiogenesis as recently reviewed (4).

Calcium entry into the cell via some TRP channels may result in localized Ca^{2+} signals that contribute to cancer cell migration (3). One example of such a localized event is referred to as Ca^{2+} flickers (27), which are highly localized (~ 5 μm diameter) and transient (10 ms – 4 s) increases in Ca^{2+} that control the direction of migration as lung fibroblasts move towards a growth factor. Ca^{2+} flickers during migration are regulated by TRPM7 (27), which may act as a stretch or mechanical sensing channel (28). With TRPM7 inhibition there is a reduction in migration of a number of cancer cell types including those of the pancreas, lung and nasopharynx (29-31).

The examples above highlight some studies where cancer cells are associated with a remodeling of TRP channel expression or where TRP channels have been linked to specific processes important in tumor progression. The interest and understanding of TRP channels in cancer is likely to expand in the coming years and these channels may represent the first class of ion channel targeted for the treatment of a specific cancer.

2. Store-operated Ca^{2+} influx

Store-operated Ca^{2+} entry is a critical Ca^{2+} influx pathway and represents the major Ca^{2+} influx mechanism in non-excitable cells (32), such as those of the epithelia from where most cancers originate. The pathway involves the activation of Ca^{2+} influx upon intracellular Ca^{2+} store depletion (32-34). The canonical components of store-operated Ca^{2+} entry are the calcium influx channel ORAI1 and the endoplasmic Ca^{2+} depletion sensor STIM1 (35,36). While this pathway has rapidly become one of the Ca^{2+}-influx pathways most studied in breast cancer, it also appears to be an important Ca^{2+} influx route during lactation (37), suggesting an important role in normal breast function.

ORAI1 and STIM1 silencing in MDA-MB-231 breast cancer cells reduces migration, invasion through Matrigel and the establishment of lung metastasis after tail vein injection in NOD/SCID mice (38), the later of which can be mimicked by the pharmacological store-operated Ca^{2+} influx inhibitor SKF96365 (38). The anti-metastasis effects of ORAI1 and STIM1 silencing appear in part due to alterations in focal adhesion turn over (38). The effects of ORAI1 silencing on breast cancer cells are not restricted to inhibition of processes important in migration, ORAI1 silencing has anti-proliferative properties in MCF-7 breast cancer cells in culture and *in vivo*. These changes may in part be due to reductions in basal Ca^{2+} influx leading to reduced ERK1/2 phosphorylation and cyclin D1 expression (39).

Alterations in the expression of specific components of store-operated Ca^{2+} entry are also a feature of some breast cancer cells. ORAI1 mRNA levels are higher in some breast cancer

cell lines compared to non-malignant breast cell lines (37). When breast cancer subtypes are stratified by gene expression, basal breast cancers (associated with a poor prognosis and a lack of effective therapies) are characterized by an elevated STIM1/STIM2 ratio. Correspondingly those patients with breast cancers with a high STIM1/STIM2 ratio and high STIM1 levels have significantly reduced survival (37), placing STIM proteins as either potential key regulators or biomarkers of breast cancer progression. The significance of STIM1 may extend beyond breast cancers given its role in the migration of cervical cancer cells (40). The mechanisms responsible for enhanced ORAI1-mediated Ca^{2+} influx in breast cancer appear to be complex and related to cancer subtypes. As discussed later in this review, in addition to STIM1-mediated activation of ORAI1, some breast cancers that overexpress the secretory pathway Ca^{2+}-ATPase 2 (SPCA2) isoform may be characterized by elevated ORAI1 mediated Ca^{2+} influx.

The ORAI1 isoform is not the only ORAI protein with a cancer association. ORAI3 protein levels and ORAI3-dependent store-operated Ca^{2+} influx are both elevated in estrogen receptor positive breast cancer cell lines (41) compared to estrogen receptor negative cell lines where store-operated Ca^{2+} influx is predominately mediated by ORAI1. A strengthening of the causative link with cancer was provided by a study in estrogen receptor positive MCF-7 breast cancer cells where ORAI3 silencing inhibited proliferation through G1 arrest (42). Although the examples above point to an upregulation of ORAI-mediated influx, some cancer types might be associated with a down regulation of this pathway that may in turn help in the acquisition of apoptotic resistance (6). Indeed, reduced ORAI1-mediated Ca^{2+} influx and expression is a feature of androgen independent prostate cancer cells, and silencing of ORAI1 reduces apoptosis in LNCaP cells (43).

This review has given examples of how ORAI1 may regulate processes important for carcinogenesis, including cell proliferation, migration and apoptosis sensitivity, and this may occur in a store-dependent or -independent manner. Examples of how ORAI1 regulates these key cancer processes are shown schematically in Figure 1.

Although not a focus of this review voltage-gated calcium channels are increasingly studied in cancer and in many cases the studies have examined the reasons for changes in expression levels in cancer. This is particularly illustrated in studies assessing mechanisms of altered expression of voltage-gated ion channels. For example, higher relapse in Wilms' tumors is associated with higher DNA copy numbers of the α1 subunit of the voltage-gated Ca^{2+} channel CACNA1E (44) and reduced expression of CACNA2D3 via promotor hypermethylation is associated with poor prognosis in gastric cancer (45). These methodological approaches will be applied to other channels and pumps and other cancers in the future.

Ca^{2+} efflux in cancer

Ca^{2+} efflux across the plasma membrane can be mediated by both Na^{+}/Ca^{2+} exchangers and primary active transport via plasma membrane Ca^{2+}-ATPases (PMCAs). However, most studies of Ca^{2+} efflux pathways in cancer cells have focused on the latter mechanism. PMCAs are encoded by 4 genes (PMCA1-4), which are alternatively spliced to generate a suite of Ca^{2+} efflux pumps responsible for maintaining resting cytosolic free Ca^{2+} at low (~ 100 nM) levels (46,47). PMCAs also contribute to specific cell functions, such as the transport of Ca^{2+} into milk through PMCA2 (48).

An area where PMCAs may be critically important in cancer is the regulation of cell death, as reflected in early work assessing the consequences of PMCA overexpression. Overexpression of some PMCA isoforms in CHO cells reduces Ca^{2+} levels within the endoplasmic reticulum and also attenuates mitochondrial Ca^{2+} accumulation after cell activation (49), a consequence which would be hypothesized to result in anti-apoptotic effects. Indeed, the overexpression of PMCA in HeLa cells increases their resistance to cell death induced by ceramide (50). Recent studies in T47D breast cancer cells shows that the overexpression of PMCA2 reduces the degree of cell death induced by ionomycin and this is associated with a reduction in the duration and magnitude of increases in $[Ca^{2+}]_{CYT}$ mediated by this Ca^{2+} ionophore (51). PMCA2 is an isoform with reported overexpression in some breast cancer cell lines (52) and in clinical human samples, where high levels appear to be

associated with a poor prognosis in some patient groups (51). Collectively these studies suggest that the remodeling of calcium efflux associated with increases in PMCA expression contributes to the acquisition of an anti-apoptotic phenotype in cancer cells.

Studies assessing the expression of PMCA isoforms during the differentiation of colon cancer cells suggest that a remodeling of PMCA isoform expression is not confined to cancers of the breast. PMCA1 expression remains fairly constant during differentiation of human colon cancer cell lines, whereas PMCA4 undergoes a pronounced increase in expression with differentiation (53,54). PMCA4 overexpression studies in HT29 colon cancer cells suggests that the down regulation of PMCA4 in colon cancer may help to augment $[Ca^{2+}]_{CYT}$ responses to proliferative stimuli without sufficiently increasing $[Ca^{2+}]_{CYT}$ to levels that promote apoptosis (55). The changes in PMCA4 expression seen in the differentiation models correlate well with human colon cancer clinical samples, where PMCA4 mRNA is reduced in colon adenocarcinomas compared to normal colon (55). The upregulation of PMCA2 expression in breast cancer and the down regulation of PMCA4 in colon cancer may seem conflicting, however, in both cases the changes in PMCA expression appear to bestow an advantage to the cancer cell, in the case of PMCA2 in breast cancer cells this appears to be related to the acquisition of greater resistance to cell death, and in colon cancer cells augmented responses to proliferative signals.

Intracellular organelle Ca^{2+} channels and pumps and cancer

Intracellular organelles play critical roles in Ca^{2+}-regulated processes either through the regulation of cytosolic free Ca^{2+} or through modulation of Ca^{2+} regulated proteins that reside within the organelle. This review will outline examples of Ca^{2+} channels and pumps of the endoplasmic reticulum and Golgi as these have been the most studied in cancer. However, the recent identification of proteins that play major roles in mitochondrial Ca^{2+} influx and efflux (56-58) and the recently identified two pore channel proteins present in endosomes (TPC1) and lysosomes (TPC2) (59) represent new opportunities to improve our understanding of the remodeling of Ca^{2+} signaling in some cancers and will no doubt be the focus of research in the future (60).

Regulators of endoplasmic reticulum Ca^{2+} levels

One of the earliest links between the regulation of endoplasmic reticulum Ca^{2+} and cancer comes from studies of the anti-apoptotic protein Bcl-2 (B cell lymphoma-2). In addition to its early and now well-established role in inhibiting the release of the pro-apoptotic factor cytochrome *c* (61-63), Bcl-2 decreases the Ca^{2+} content of the endoplasmic reticulum (50,64,65). Mechanistically this occurs at least in part through interaction with the IP_3 receptor (66), likely reducing the ability to achieve the high Ca^{2+} loads required for mitochondria to accumulate Ca^{2+} sufficiently to trigger apoptotic cell death (67). Some examples of alterations in the expression of key calcium channels and pumps of the endoplasmic reticulum are highlighted in Table 1. Similar to increases in the expression of PMCA4 during colon cancer cell line differentiation and the down regulation of PMCA4 expression in some colon cancers, SERCA3 pump expression increases with the differentiation of colon cell lines, and is down regulated in colon cancer (68), implicating a major remodeling of active Ca^{2+} transport in colon cancer. The significance of the down regulation of SERCA3 is not restricted to colon cancer, given the more recent report of a significant down regulation of SERCA3 in breast cancers, an event that is even seen in benign lesions (69). Further evidence of the potential significance of SERCA down regulation in cancer is reflected in studies of mice haplodeficient for SERCA2 (70,71). These mice are characterized by increased incidence of squamous cell tumors, the mechanism of which likely involves altered Ca^{2+} signaling and a subsequent change in the microenvironment of skin epithelia (70).

Regulators of Golgi Ca^{2+} levels

Although more recently identified and less widely studied in the context of contributions to

cellular processes than SERCAs, secretory pathway Ca^{2+}-ATPases (SPCAs), both the ubiquitously expressed SPCA1 isoform and the more restricted SPCA2 isoform (72,73), are beginning to be assessed in cancer cells.

In MDA-MB-231 basal-like breast cancer cells (that do not express the SPCA2 isoform), SPCA1 silencing inhibits proliferation without changes in global $[Ca^{2+}]_{CYT}$, consistent with the minor role of SPCAs (c.f. PMCAs and SERCAs) in contributing to $[Ca^{2+}]_{CYT}$ recovery in most cell types (74). Instead, as may be the case for other Ca^{2+} channels and pumps located on the membranes of intracellular organelles, the mechanism by which SPCA1 silencing inhibits proliferation may involve alterations in the Ca^{2+} levels within the Golgi lumen where Ca^{2+} regulated enzymes reside. Indeed, one consequence of SPCA1 silencing in MDA-MB-231 breast cancer cells is the inhibition of cleavage of pro-IGF1R likely through reduced activity of the Ca^{2+}-sensitive pro-protein convertase Furin (74). The consequences of reduced SPCA1-mediated Ca^{2+} sequestration may be cell type and context dependent as shown by the increased susceptibility of $Spca1^{+/-}$ mice to develop squamous skin tumors (75).

One of the proposed roles for the other secretory pathway Ca^{2+} ATPase isoform, SPCA2, has been the sequestration of Ca^{2+} during lactation (76), however, this pump also appears to play a role in the pathophysiology of breast cancer. SPCA2 levels are increased in luminal-like breast cancer cell lines and clinical breast cancers belonging to the Luminal B and ERBB2 molecular subtypes (39). This may be related to hormonal factors given that in MCF-7 breast cancer cells SPCA2 mRNA levels increase with prolactin (77). Silencing of SPCA2 in breast cancer cell lines that overexpress this Ca^{2+} pump, such as MCF-7 cells, reduces their proliferation, anchorage independent growth and growth *in vivo* (39). However, in contrast to SPCA1 in breast cancer cells, SPCA2 does not appear to contribute to tumor progression through alterations in Ca^{2+} levels within the Golgi. In a result which was initially counter intuitive, SPCA2 overexpression increases basal $[Ca^{2+}]_{CYT}$, rather than decreasing it as might be expected for a calcium pump that sequesters Ca^{2+} from the cytoplasm into the Golgi. Overexpression of SPCA2 leads to its localization at the plasma membrane where it activates ORAI1 channels, the consequence of which is activation of the transcription factor NFAT (shown in Figure 1A) (39). SPCA2 overexpression-induced increases in Ca^{2+} influx across the plasma membrane represents an example where the contribution that a calcium pump makes to tumor progression is not directly related to its own Ca^{2+} transporting ability. The ability of SPCA2 to contribute to tumor growth independently of its own Ca^{2+} transporting ability suggests that pharmacological inhibitors of SPCA2 Ca^{2+} transport function may be ineffective in breast cancers where SPCA2 solely contributes to tumor growth through this ORAI1-dependent mechanism and demonstrates the importance of mechanistic studies assessing the contribution of Ca^{2+} channels and pumps to tumorigenic pathways.

Calcium signaling and cancer – new horizons

Major advances have occurred in the last decade in our understanding of how calcium signaling is remodeled in some cancer cells and how specific calcium channels or pumps represent potential new therapeutic targets in oncology. However, there are areas of cancer research where the link between calcium signaling is still relatively unexplored, such as the "emerging hallmarks of cancer" recently described by Hanahan and Weinberg (78). These include cellular energy metabolism reprogramming, whereby cancer cells shift their energy metabolism to glycolysis, a phenomenon first described by Otto Warburg almost a century ago (78-80). Further studies on the possible role of Ca^{2+} signaling in the regulation of glycolysis, the switch to glycolysis and the use of glycolysis generated ATP to fuel Ca^{2+} pumps in cancer cells is required (81,82). Another aspect of cancer biology where Ca^{2+} signaling is clearly going to be critical but has not been fully explored is the tumor microenvironment (78). Due to the depth of work in the area of tumor microenvironment readers are encouraged to consult the numerous reviews on this topic (83-85). An aspect of the tumor microenvironment where signaling is likely to be particularly significant is cancer associated fibroblasts, which are in an "activated" state and are in a dynamic signaling interplay with cancer cells (78,86). Ca^{2+} may be critical to this signaling as reflected by the importance of PDGF in the signaling between cervical cancer cells and cancer associated

fibroblasts (87) and the ability of PDGF to elevate $[Ca^{2+}]_{CYT}$ in other cell types (88).

Conclusions

Many processes contribute to cancer development and Ca^{2+} signaling seems to play a role in many of them. Numerous studies have now established that some cancers are associated with major changes in the expression of specific Ca^{2+} channels and pumps, and that inhibition of some of these proteins inhibits the proliferation and/or metastasis of cancer cells. The next decade will see the role of Ca^{2+} in cancer further defined and may see agents that specifically target Ca^{2+} channels or pumps used in cancer therapy.

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FOOTNOTES.

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Abbreviations: Bcl-2, B cell lymphoma-2; $[Ca^{2+}]_{CYT}$, cytosolic calcium; ERK, extracellular signal-regulated kinase; IGF1R, insulin-like growth factor receptor; NFAT, nuclear factor of activated T cells; PDGF, platelet-derived growth factor; PMCA, plasma membrane calcium ATPase; SERCA, sarcoplasmic/endoplasmic reticulum calcium ATPase; SPCA, secretory pathway calcium ATPase; STIM, stromal interaction molecule; TPC, two-pore channel; TRP, transient receptor potential.

FIGURE LEGEND.

Figure 1—ORAI1 regulates processes important for cancer cell proliferation, migration and apoptosis.
A) In MCF7 human breast cancer cells SPCA2 partially localizes to the plasma membrane and interacts with ORAI1 to mediate store-independent Ca^{2+} influx. This is associated with phosphorylation of extracellular signal-regulated kinase-1/2, nuclear translocation of NFAT and increased cell proliferation (39). **B**) Silencing of ORAI1 or STIM1 in MDA-MB-231 human breast cancer cells reduces store-operated Ca^{2+} influx and is associated with reduced focal adhesion turnover, cell migration and metastasis formation *in vivo*. Expression of constitutively active Ras or Rac in these cells partially rescues impaired focal adhesion turnover and cell migration induced by inhibition of store-operated Ca^{2+} entry, implicating possible roles for these small GTPases in Ca^{2+}-dependent cell migration (39). **C**) In LNCaP human prostate cancer cells ORAI1 expression is regulated by the androgen receptor (AR) and ORAI1 silencing is associated with resistance to thapsigargin (TG), tumor necrosis factor α (TNFα), cisplatin and oxaliplatin -induced apoptosis (43). In panel A and B (black) ORAI1 expression may *promote* carcinogenesis; in panel C (red) ORAI1 expression may *inhibit* carcinogenesis (i.e. promote apoptosis).

Table 1: Examples of altered expression of calcium channels and pumps in human cancers

Ca^{2+} pump or channel	Cancer type	Change with cancer		Reference
		mRNA	Protein	
Transient receptor potential channels				
TRPC1	Breast cancer: patient tissue samples	↑	↑	(89)
TRPC3	Ovarian cancer: patient tissue samples		↑	(23)
	Breast cancer: patient tissue samples	↑		(22)
TRPC6	Esophageal cancer: patient tissue samples	↑	↑	(24)
	Glioma: patient tissue samples	↑	↑	(25)
	Liver cancer: patient tissue samples	↑	↑	(90)
	Breast cancer: patient tissue samples	↑	↑	(22,89)
TRPM7	Pancreatic cancer: patient tissue samples	↑	↑	(29)
	Breast cancer: patient tissue samples	↑	↑	(89)
TRPM8	Pancreatic cancer: cell lines (mRNA) & patient tissue samples (protein)	↑	↑	(91)
	Prostate cancer: cell lines & patient tissue samples	↑	↑	(8,17,92)
	Breast cancer: patient tissue samples	↑	↑	(8,89)
	Melanoma: patient tissue samples	↑		(8)
	Colorectal cancer: patient tissue samples	↑		(8)
	Lung cancer: patient tissue samples	↑		(8)
TRPV1	Bladder cancer: patient tissue samples	↓	↓	(93)
	Prostate cancer: patient tissue samples	↑	↑	(94)
TRPV6	Breast cancer: patient tissue samples	↑	↑	(18,21,89,95)
	Prostate cancer: patient tissue samples	↑	↑	(18,95)
	Thyroid cancer: patient tissue samples		↑	(95)
	Colon cancer: patient tissue samples		↑	(95)
	Ovarian cancer: patient tissue samples		↑	(95)
Voltage-gated calcium channels				
Cav1.2	Colon cancer: patient tissue samples	↑		(96)
Cav3.2	Prostate cancer: patient tissue samples	↔	↑	(97)
Store-operated calcium channels				
ORAI1	Breast cancer: cell lines	↑	↔	(37,41)
ORAI3	Breast cancer: cell lines & patient tissue samples (mRNA only)	↑, ↔	↑	(37,41,42)
Plasma membrane calcium ATPases				
PMCA2	Breast cancer: cell lines (mRNA only) & patient tissue samples	↑	↑	(51,52)
PMCA4	Colon cancer: patient tissue samples	↓		(55)
Store release channels				
IP3R1	Glioblastoma: patient tissue samples	↓		(98)
IP3R3	Glioblastoma: patient tissue samples	↑		(98)
	Colorectal cancer: patient tissue samples		↑	(99)
Sarcoplasmic/endoplasmic reticulum calcium ATPases				
SERCA2	Oral cancer: cell lines (mRNA only) & patient tissue samples	↓	↓	(100)
SERCA3	Colon cancer: cell lines & patient tissue samples		↓	(68)
	Breast cancer: patient tissue samples		↓	(69)
Secretory pathway calcium ATPases				
SPCA1	Breast cancer: basal-like clinical samples & cell lines	↑		(74)
SPCA2	Breast cancer: cell lines & patient tissue samples (mRNA only)	↑	↑*	(39)

↑: increase; ↓: decrease; ↔: no significant difference; *MCF-7 vs MCF-10A

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Figure 1